Industrial Disease Standards Panel

Comité des normes en matière de maladies professionelles

REPORT TO THE WORKERS' COMPENSATION BOARD ON OCCUPATIONAL EXPOSURE TO PCBs

88-04657/

The Industrial Disease Standards Panel is a Schedule 1 Agency of the Government of Ontario attached to the Ministry of Labour. The function of the Panel, as defined in Section 86p of the Workers' Compensation Act of Ontario, is as follows:

(a) to investigate possible industrial diseases;

(b) to make findings as to whether a probable connection exists between a disease and an industrial process, trade or occupation in Ontario;

(c) to create, develop and revise criteria for the evaluation of claims respecting industrial diseases; and

(d) to advise on eligibility rules regarding compensation for claims respecting industrial diseases.

The Panel is required by statute to report its findings to the Workers' Compensation Board of Ontario.

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Industrial Disease Standards Panel
10 King Street East, 7th Floor
Toronto, Ontario M5C IC3
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REPORT TO THE WORKERS' COMPENSATION BOARD

ON

OCCUPATIONAL EXPOSURE TO PCBs AND VARIOUS CANCERS

Industrial Disease Standards Panel

IDSP Report No. 2

Toronto, Ontario

December, 1987

REPORT TO THE WORKERS' COMPENSATION BOARD

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OCCUPATIONAL EXPOSURE TO PCBs AND VARIOUS CANCERS

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Ontario Ministry of Labour
Ministère du Travail de l'Ontario

Industrial Disease Standards Panel
Comité des normes en matière de maladies professionelles

10 King Street East
7th Floor
Toronto, Ontario
M5C 1C3
416/965-5056

December 9, 1987

Dr. R. G. Elgie
Chairman
Workers' Compensation Board
2 Bloor Street East, 20th Floor
Toronto, Ontario
M4W 3C3

Dear Dr. Elgie:

In a letter dated May 27, 1986, the Board requested the Industrial Disease Standards Panel to respond to a number of questions about the occurrence of various cancers among workers in Ontario with occupational PCB exposures.

The Panel is pleased to send to the Board its Report of Findings in this matter in accordance with Section 86p(10) of the Workers' Compensation Act. The Panel is in unanimous agreement concerning all of the conclusions contained herein on findings of probable connection, associated eligibility rules and recommendations for the development of exposure registries for workers occupationally exposed to PCBs.

Other than for liver, biliary tract and gall bladder cancers, the Panel found no conclusive evidence of a probable connection between occupational PCB exposure and any other site specific cancer. Nevertheless, the Panel intends to review new evidence as it becomes available concerning the possibility of such relationships.

The Panel will be pleased to respond to questions the Board may have about its findings.

Yours sincerely,

James M. Ham

James M. Ham
Chairman

JMH/med

Encl.

Ontario
Ministry of
Labour

Ministère
du Travail
de l'Ontario

Industrial Disease
Standards Panel

Comité des normes
en matière de maladies
professionelles

10 King Street East
7th Floor
Toronto, Ontario
M5C 1C3
416/965-5056

December 3, 1987

MEMORANDUM TO: WORKERS' COMPENSATION BOARD

FROM: INDUSTRIAL DISEASE STANDARDS PANEL

RE: **REPORT ON OCCUPATIONAL EXPOSURE TO PCBs AND VARIOUS CANCERS**

1.0 ISSUES AND FINDINGS:

1.1 In a letter dated May 27, 1986, the Workers' Compensation Board requested that the Panel consider the issue of the human carcinogenicity of PCBs; and that the Panel include in its deliberations the following questions:

1. As a matter of policy, should the WCB accept entitlement for those workers who have been occupationally exposed to PCBs and who have subsequently developed:

   a) A primary liver cancer (hepatocellular carcinoma);

   b) Cancer involving other organs.

2. If the answer to question 1.b) is yes, then

   a) What types of cancer should be accepted for entitlement?

   b) If there are some cancers considered to arise from occupational exposure to PCBs, what eligibility rules (e.g. route of exposure, duration and intensity of exposure, appropriate latency period) should be fulfilled in order for entitlement to be accepted?

   c) Under what circumstances would it be unlikely that occupational exposures to PCBs produce the cancers under investigation?

d) Should the compensation approach be founded upon a statutory schedule, a policy guideline or on a case by case adjudication basis?

3. At the present time the WCB Industrial Physicians maintain a list of surveillance claims for individuals who have had PCB exposure but no detected ill health effect. This list is held by the WCB and can be reassessed at any time should health effects become apparent. Does the Panel consider that this is a reasonable method of maintaining a register of possible future claimants?

1.2 The Report of the Special Panel (Appendix A) reviews the evidence from both animal and epidemiological studies of the possible carcinogenicity of PCB exposure. The epidemiological material includes the grouping together into a 'meta-analysis' of the mortality experience of electrical capacitor manufacturing workers exposed to PCBs in five different plants from three countries (U.S.A., Sweden and Italy). The data for the meta-analysis is derived from four historical prospective cohort studies (Brown et al., 1986; Bertazzi et al., 1987; Gustavsson et al., 1987; and Nicholson et al., 1987).

1.3 When the cohorts are combined in a meta-analysis (Appendix A, Table 18), compelling epidemiological evidence of excess cancers appears for the liver, biliary tract and gall bladder (ICD 155 and 156). Moreover, for the liver, biliary tract and gall bladder cancers, there is evidence of increasing risk with increasing total plant employment, a surrogate for dose or exposure level (Appendix A, Table 23). Using a model linking the relative risk of liver cancer with estimated body burdens of PCBs to group the data for the liver, biliary tract and gall bladder cancers, there is corroboration for the time and exposure relationships with cancer risks (Appendix A, Table 24).

1.4 There is strong support from animal studies of the induction of hepatocellular and extra-hepatic biliary tract carcinomas from PCB ingestion, especially when exposure duration is long enough (over one year) and when exposures involve the more highly chlorinated PCBs. Moreover, all chronic animal studies (with the exception of studies using dogs) have demonstrated that PCB exposure, especially from the more highly chlorinated PCBs, produces precancerous lesions which other studies suggest may be precursors of hepatocellular carcinomas. In addition, there is animal evidence to support the notion of PCB action as both a promoter and an initiator of hepatocellular carcinomas. However, there is support only for the promotional action of PCBs in the production of liver cancers in the human epidemiology. Lastly, there is support for the linkage of PCB exposure with liver, biliary tract

and gall bladder cancers from the similarity of results from human exposure to chemical compounds with molecular structures similar to those for PCBs.

1.5 For all of the above reasons, the Panel makes the following finding:

FINDING 1: AT THIS TIME, THE PANEL FINDS A PROBABLE CONNECTION BETWEEN LIVER, BILIARY TRACT AND GALL BLADDER CANCERS AND OCCUPATIONAL EXPOSURE TO PCBs.

1.6 Further examination of the combined cohorts (Appendix A, Table 18) shows non-statistically significant evidence of excess cancers for the lymphomas (ICD 200-203) which is concentrated exclusively among female workers (Appendix A, Table 17). However, two of the lymphomas in females occurred within two years of the commencement of plant employment (Appendix A, pg. 41 and Table 25) and a third within four years of first employment (Appendix A, Tables 25 and 27a). It is unlikely, therefore, that these malignancies could have been associated with PCB exposure. Elimination from further consideration of deaths from lymphomas arising within the first five years of plant employment reduces the estimate of risk of mortality from lymphomas from 161 to 138. Moreover, all the excess lymphomas are clustered among the female workers (Appendix A, Tables 17 and 27a); but the reordering of female lymphoma observed and expected deaths using hypothetical risk categories (Appendix A, Table 28a) does not show a gradient of increasing risk with increasing duration of exposure and time from onset. Although there is a suggestion of increasing risk when the data for lymphomas and leukaemias, tabulated according to duration of exposure and to time from onset, is ordered using hypothetical risk categories (Appendix A, Table 28), this finding is weakened by the fact that the significant number of cases in the highest risk categories includes leukaemias some of which had the least exposure (Appendix A, pg.43). Moreover, there is only limited support from animal evidence for the lymphomas. The Panel finds, therefore, that the evidence concerning lymphomas remains only suggestive, and not conclusive (Appendix A, pg.43).

1.7 The Panel has reviewed reported evidence of dermal cancers among capacitor manufacturing workers. However, no cluster of cases was found (only a possible 4 out of 326 workers) which would allow the raising of the hypothesis that dermal cancers are related to occupational PCB exposure. Moreover, there is no supporting animal evidence for this opinion. Given the prevalence of cancer, and particularly skin cancer, in our society, the Panel has decided that there is no evidence at this time of which it is aware that occupational PCB exposure is associated with increased risk of dermal cancer.

1.8 The Panel did not find convincing epidemiological evidence of a relationship between any other site-specific cancers and PCB exposure.

FINDING 2: AT THIS TIME, THE PANEL DOES NOT FIND A PROBABLE CONNECTION BETWEEN ANY OTHER SITE-SPECIFIC CANCERS AND OCCUPATIONAL EXPOSURE TO PCBs.

1.9 Nevertheless, the Panel notes that there remain questions concerning a relationship between lymphomas and PCB exposure. The Panel intends to review the issue of any relationship between cancers other than liver, gall bladder and biliary tract cancer and PCB exposure when further evidence becomes available.

1.10 The Board has, in a separate communication, requested advice on the matter of the 'healthy worker effect'. The Panel has not as yet responded on this issue and it is not considered further in this document.

2.0 ELIGIBILITY RULES:

2.1 There remains the difficult issue of defining, from among the excess liver, biliary tract and gall bladder cancers, the most likely sub-groups to have PCB-related occupational cancers. Primary liver cancer is a rare form of cancer in developed countries, accounting for about four deaths annually for every 100,000 people living, or about 0.6% of the deaths every year (about 2.6% of all cancer deaths). For this reason alone, the number of occupationally related liver cancer cases for any given exposure circumstance is bound to also be small.

2.2 To establish appropriate eligibility rules for determining the validity of a PCB-related occupational liver cancer claim, recourse is made to the evidence shown in Appendix A, Table 23. The first rule incorporates the use of exposure durations and latency periods the application of which rules out the possibility that the cancer in question was not due to occupational origins. None of the reported liver, biliary tract and gall bladder cancers occurred with less than 3 months' duration of exposure nor within 5 years from first exposure (Appendix A, Tables 22 and 23). With this evidence in hand, the Panel proposes the following rule:

ELIGIBILITY RULE 1: THAT CLAIMS ARISING FROM LIVER, BILIARY TRACT AND GALL BLADDER CANCERS AMONG WORKERS FOR WHOM THE DURATION OF OCCUPATIONAL PCB EXPOSURE WAS AT LEAST 3 MONTHS, AND WHERE THE LATENCY PERIOD (FROM FIRST EXPOSURE TO DIAGNOSIS) WAS AT LEAST 5 YEARS, BE COMPENSATED.

2.3 The Panel has had its attention drawn to the possibility of short intense exposures to PCBs arising from sudden and unusual work circumstances such as PCB fires or explosions. In these instances and in others where dispute arises concerning the application of the above eligibility rule the use of blood serum measurements of PCB concentrations in instances where these tests can be made is recommended. Accepted methods for analysing blood samples (see, for example, the Nazar, M.A. communication to Panel dated 1987 11 02 concerning the Ministry of Labour's method for measuring PCB concentrations in blood serum samples (Appendix B)) can be applied as follows:

ELIGIBILITY RULE 2: WHERE DISPUTE ARISES IN THE APPLICATION OF ELIGIBILITY RULE 1 AND CIRCUMSTANCES PERMIT, CLAIMS ARISING FROM LIVER, BILIARY TRACT AND GALL BLADDER CANCERS AMONG WORKERS FOR WHOM THE BODY BURDEN OF PCBs AS MEASURED BY PCB BLOOD SERUM CONCENTRATIONS IS SIGNIFICANTLY HIGHER THAN THE NORMAL BACKGROUND DISTRIBUTION OF PCB BLOOD SERUM CONCENTRATIONS IN THE GENERAL POPULATION, BE COMPENSATED.

3.0 WORKER EXPOSURE HISTORIES AND ADDITIONAL INFORMATION:

3.1 The Board has asked the Panel for advice concerning the maintenance of a register of possible future claimants with PCB exposure. The Panel considers the maintenance of a list of surveillance claims inadequate.

3.2 It is critically important both to the prevention of industrial disease and to socially just compensation of such disease that registers of exposure histories for toxic substances and agents be developed and maintained. The subject of PCB exposures is an appropriate instance in which to invoke this principle. The Panel therefore recommends that:

RECOMMENDATION 1: THE BOARD, TOGETHER WITH OTHER APPROPRIATE ORGANIZATIONS, PRIVATE AND PUBLIC, ESTABLISH A COMPLETE REGISTER OF WORKERS WITH OCCUPATIONAL PCB EXPOSURES.

RECOMMENDATION 2: THAT THIS REGISTER CONTAIN, FOR EACH SUCH WORKER, AS COMPLETE A RECORD AS IS REASONABLY POSSIBLE OF ALL PLANT EMPLOYMENTS AND EXPOSURE CIRCUMSTANCES (INCLUDING DURATION AND INTENSITY WHERE AVAILABLE) WHERE PCB EXPOSURES TOOK PLACE.

3.3 In its investigations and findings, the Panel intends to report on

the adequacy of available information on worker exposures to toxic substances and agents.

3.4 The evidentiary base for the Panel's investigation is shown in Appendix B. Appendix C concerning PCB usage in Ontario is provided to assist in the adjudication of individual case claims.

APPENDIX A

REPORT OF THE SPECIAL PANEL

ON

OCCUPATIONAL PCB EXPOSURE AND VARIOUS CANCERS: HUMAN HEALTH EFFECTS AND CARCINOGENIC RISK POTENTIAL OF PCBs

REPORT OF THE SPECIAL PANEL ON OCCUPATIONAL PCB EXPOSURE AND VARIOUS CANCERS: HUMAN HEALTH EFFECTS AND CARCINOGENIC RISK POTENTIAL OF PCBs

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FOREWORD

The Special Panel was chaired by Dr. William Nicholson, Division of Environmental and Occupational Medicine, Mount Sinai School of Medicine, New York.

ACKNOWLEDGEMENTS

The contributions of Pier Bertazzi, David Brown and Per Gustavsson, who performed additional analyses on the data for their cohorts and supplied supplementary information for inclusion in this report, are gratefully acknowledged.

SECTION 1

EXPERIMENTAL ANIMAL STUDIES

1.1 INTRODUCTION

A large number of studies have evaluated the potential carcinogenic effect of polychlorinated biphenyls (PCBs) in a variety of animal species and exposure circumstances. Virtually all of these studies have focused on liver carcinogenesis and on the effect of PCBs either to induce cancer directly or to modulate the response of other liver carcinogens. The earliest study (Ito et al., 1973) demonstrated that highly chlorinated PCBs induced hepatocellular carcinomas in mice and promoted the carcinogenic effect of benzene hexachloride in the same species. A variety of subsequent studies (See Section 1.4, Experimental PCB carcinogenesis studies, below) have confirmed these basic findings. The emerging data suggest that the role of PCBs in the development of hepatocellular carcinoma is a highly complex one. They may act as promoters of cells initiated either by other previously administered carcinogens or spontaneously. They may also enhance or inhibit carcinogenesis by virtue of their stimulation of liver enzymes, which, in turn, can alter the metabolism of subsequently administered carcinogens. PCBs appear to have little or no genotoxic effect. They are negative in the Ames Salmonella test (Heddle and Bruce, 1977: McMahon et al., 1979), the micronucleus test (Heddle and Bruce, 1977), the V79 Chinese hamster assay (Hattula, 1985), and do not produce chromosomal alterations (Hoopingarner et al., 1972) nor dominant lethal mutations in rats (Green et al., 1975).

In as much as PCBs may play a direct role in cancer promotion and an indirect one in cancer initiation, it is appropriate to review briefly the data on cancer initiation and promotion in general in order to appreciate the observed effects in animals and the potential effects in humans. Virtually all PCB studies have been concerned with hepatocellular carcinogenesis and, thus, the following brief review of initiation-promotion data will focus on liver cancer from chemical exposures. To the extent that the mechanism of action of PCBs is similar in human and animal species, the data on experimental carcinogenesis is important for the determination of the appropriate analysis of epidemiological studies of individuals exposed to PCBs. Further, in order to appreciate fully the role of PCBs as cancer risk modifiers in liver tumor development, we will also briefly review the existing information on the various liver changes associated with hepatocarcinogenesis and the effect of the various PCBs on the induction of liver enzymes that might alter the metabolism of externally administered carcinogenic agents.

1.2 INITIATION AND PROMOTION EFFECTS IN HEPATOCARCINOGENESIS

A multistage model of carcinogenesis has long been extant. Berenblum and Shubik (1947) first demonstrated that chemically induced skin carcinogenesis could be separated into initiation and promotion stages. Their experiments with croton oil showed that the effect of an initiating carcinogen could be greatly enhanced by the later application of a promoting agent, which by itself was non-carcinogenic. Application of a promoter prior to an initiator had a substantially reduced effect. Subsequently, initiation and promotion effects have been demonstrated in the development of cancer in a wide variety of tissues, including the liver (Farber, 1973). The initial two-stage model has been extended to include multiple proliferation and promotional stages (Slaga, 1983).

A multistage model of carcinogenesis has also been suggested for human cancer, based on the observed power law dependence of cancer incidence at a variety of sites (Fisher and Holloman, 1951; Armitage and Doll, 1954; 1957; Doll, 1978). The models have ranged from proposals of multiple (up to six or seven) mutations (or carcinogenic events) occurring in the same or adjacent cells (Fisher and Holloman, 1951; Nordling, 1953) to models that involved preferential clonal development of altered cell lines (Armitage and Doll, 1957; Fisher, 1958). Some or all of the stages may be effected by external carcinogens. For those stages susceptible to action by an external carcinogen it would be expected that the probability of progression to the next stage would be proportional to the time that an agent, or its active metabolite, is at a reaction site. A constant exposure to environmental carcinogens would then introduce a power of time for each stage that is effected by a particular external agent. It would also introduce a power of dose. Stages that depend upon spontaneous changes occurring randomly in time also introduce a power of time for each such stage. While the model is a statistical one, based upon the age dependence of cancer, it makes explicit predictions for the age, dose and time dependence of cancer from external agents. Although direct evidence of initiation and promotion is unavailable in humans, the time courses of certain occupationally induced cancers are in accord with the model's predictions and suggest late stage or promotional action for some and early stage or initiational action for others (Day and Brown, 1980).

A number of distinct pathological phenomena (or stages) have been identified in the development of hepatic carcinoma. (See Pitot and Sirica, 1980, for a good review.) These include the development of foci of cellular alteration or "liver islands", areas of colangiofibrosis, and neoplastic nodules (Squire and Levitt, 1975). The foci are areas devoid of glucose-6-phosphatase, canalicular adenosine triphosphatase and beta-

glucuronidase activity. They also typically demonstrate the presence of gamma-glutamyl transpeptidase (GGTP). The cells in these regions are indistinguishable from normal hepatocytes except through special staining techniques. The areas of colangiofibrosis or "bile duct proliferation" are characterized by foci or areas of hyperbasophilic, atypical ducts in a fibrous stroma, usually with excess collagen formation. The neoplastic or "hyperplastic" nodules, sometimes referred to as hepatomas, are distinct spherical lesions containing substantially altered cells. There usually is a sharp demarcation of the lesion from the surrounding, unaffected liver. (Note that the terminology differs from that which is commonly used to describe human liver tumors; in humans "hepatoma" is synonymous with hepatocellular carcinoma.) Each of the above appear well before the development of hepatocellular carcinoma induced by external agents.

It has been found that the numbers of enzyme altered foci or neoplastic nodules may decrease following cessation of a carcinogenic exposure (Teebor and Becker, 1971), suggesting some regression of promotional effects. However, not all nodules totally regress and cells within those which have regressed continue to demonstrate the presence of a "preneoplastic" antigen (Farber, 1976), indicating the presence of a permanent cellular alteration. Further, in some circumstances, it has been demonstrated that the enzyme-altered foci appear to be clonal developments of single altered cells (Scherer and Hoffmann, 1971).

While the studies are not completely definitive, a useful model for the description of hepatocellular carcinoma considers the development of the altered foci and neoplastic nodules to be early stages in the carcinogenesis process. Exposure to an initiating carcinogen leads to altered cells, some of which may develop into the foci, subsequently into neoplastic nodules and, perhaps, ultimately into hepatocellular carcinoma. The development of foci, neoplastic nodules and frank carcinoma is enhanced by the administration of various promoting agents. After administration of a promoting chemical ceases, but prior to the development of carcinoma, regression of the preneoplastic lesion can occur, with a concomitant reduction in cancer risk. However, cells within that lesion may still contain a memory of prior alteration that may again be stimulated to progress to hepatocellular carcinoma. Among the agents that have been especially effective in promoting liver cancer in rodents are phenobarbital (PB), dichlorodiphenyltrichloroethane (DDT) and PCBs (Peraino et al., 1973; 1975; Nishizumi, 1979). Because of the strong relationship of preneoplastic lesions with hepatocellular carcinoma, many studies investigating initiation-promotion activity within the liver did so on the basis of these changes rather than on the results of the much longer studies of carcinoma development.

1.3 BIOCHEMICAL EFFECTS OF PCBS AND SIMILAR CHEMICALS

Among other effects, PCBs are potent inducers and inhibitors of various liver enzymes (Litterst et al., 1972; Chen and DuBois, 1973; Safe et al., 1985). In this activity there is a wide variability among the effects of different PCB isomers present in the commercial mixtures. It would appear that many PCB isomers exhibit a "mixed-type" induction pattern reflecting induction properties that simulate both PB and 3-methylcholanthrene (3-MC). It has been found that treatment of rats with PB-type inducers enhances the production of several cytochrome P-450-dependent monooxygenases and cytochromes P-450a, P-450b and P-450e. In contrast, 3-MC induces different monooxygenases and cytochromes P-450a, P-450c and P-450d. All of the above cytochromes, as well as the PB and 3-MC monooxygenases are induced by Aroclor 1254. This enzyme induction capability of the PCBs is of considerable significance in that many of the induced monooxygenases play a role in the metabolism of various other carcinogenic chemicals. The enzyme inducing activity of PCBs is mimicked, but at much lower concentrations, by the chlorinated dibenzofurans (CDFs) and chlorinated dibenzodioxins (CDDs).

Extensive work with 2,3,7,8 tetrachlorodibenzodioxin (TCDD) has provided some understanding of the mechanism of action of these compounds (Poland et al., 1979; 1983). In addition to the induction of the above enzymes, it is found that the halogenated aromatic hydrocarbons, especially TCDD, are potent inducers of aryl hydrocarbon hydroxylase (AHH) and that the toxicity of the various isomers of the PCBs, CDDs and CDFs strongly correlates with AHH inducibility. A binding receptor for TCDD and other chlorinated hydrocarbons, the Ah locus, in the liver cytosol has been identified, to which the binding affinity is directly proportional to AHH inducibility and isomer toxicity. This suggests that many of the effects of the CDDs, the CDFs and the PCBs are mediated through this receptor. Binding to the Ah locus is found to be greatest for planar molecules of the size of TCDD (3 x 10 Angstroms). Of the PCBs, the congeners, 3,3'4,4'-tetra-, 3,3',4,4',5-penta- and 3,3',4,4',5,5'-hexa- are approximately isosteric with TCDD and are the most toxic. Thus, the greater activity of the higher chlorinated isomers, especially those having a planar structure, and the similarity of action of the PCBs, the CDFs and the CDDs can be understood on the basis of molecular structure.

1.4 EXPERIMENTAL PCB CARCINOGENESIS STUDIES

Eight studies provide direct evidence of the carcinogenic potential of PCBs in rodents. However, the numbers of animals in most study groups were relatively small (less than 50) and several of the studies only followed animals for a limited portion of

their life span (as short as 32 weeks). Nevertheless, the studies demonstrate reasonable consistency. Differences in tumor or foci incidence between studies are understandable in terms of the differences in dosage, durations of exposure and follow-up, species sensitivity and degrees of PCB chlorination. As with general toxicity, the higher chlorinated PCBs (penta- or hexa-) are the more carcinogenic. Data on relative carcinogenicity of a particular compound in different species are lacking. However, in terms of gross toxicity, guinea pigs and chickens appear to be the most sensitive species, with rats, monkeys, mice, rabbits and hamsters increasingly more resistent to the toxic effects of PCBs (McConnell, 1985). Table 1 lists the equitoxic levels of various halogenated aromatic compounds in the food of rhesus macaques (McNulty, 1985). Additionally, sex differences may be manifest. While the above generalities can be stated, the data on species or sex sensitivity for any specific toxic effect are extremely limited.

Virtually all studies of PCB effects have been conducted with commercial mixtures of Aroclor (U.S. manufacture) and Kanechlor (Japanese manufacture). Table 2 lists the approximate composition of various mixtures of these products along with measured CDF contamination levels. In contrast to the 1-20 ppm CDF contamination of newly manufactured PCBs, the contamination of the PCBs in the "Yusho" rice oil was about 5000 ppm (Kuratsune et al., 1976).

Mice

The first study on PCB-induced liver tumorigenesis is that of Ito et al. (1973), who fed dd male mice a diet to which 500, 250, or 100 ppm of Kanechlor 300, Kanechlor 400 or Kanechlor 500 had been added. Neoplastic nodules and hepatocellular carcinomas were seen after 32 weeks only in the group exposed to 500 ppm of Kanechlor 500 in their diet. There, seven of twelve animals were found to have neoplastic nodules and five of twelve, hepatocellular carcinomas.

In a second study of mice, administration of 300 ppm of Aroclor 1254 in the diet of mice for 11 months led to the development of hepatomas (neoplastic nodules) in ten of 22 surviving mice (Kimbrough and Linder, 1974). One of 24 mice fed the same diet for six months, followed by a five months recovery period, also demonstrated hepatomas. No evidence of hepatocellular carcinoma was present.

Rats

Kimura and Baba (1973) fed a varying diet of Kanechlor 400 to groups of ten male and female Donyru rats for a total of 32 weeks.

Neoplastic nodules were found in all six female rats fed a total of 1200 mg or more of PCB in their diet. No such changes were found in female rats fed 1100 mg or less or in any males fed up to 1800 mg of PCB. However, fatty degeneration was found in all study rats ingesting from 450 mg to 1800 mg of Kanechlor 400.

Ito et al. (1974) also studied the effect of PCBs on rats. Table 3 lists the liver lesions found in rats fed varying amounts of Kanechlor 500, Kanechlor 400 and Kanechlor 300. As can be seen, all three Kanechlors produced liver changes related to the concentration in the diet. Again, the results were limited as the periods of exposure and observation were only for 52 weeks.

One of the more extensive studies of PCB carcinogenesis is that of Kimbrough et al. (1975), who exposed animals to 100 ppm Aroclor 1260 in their diet from three weeks to 22 months. The experimental group consisted of 184 female Sherman rats and tissues from a wide variety of organs were examined microscopically. The results of this study are shown in Table 4 and demonstrate a substantially increased incidence of hepatocellular carcinoma among the experimental animals (26/184 versus 1/173 in controls). Additionally, neoplastic nodules were found in 124 of 184 animals and altered foci in 182. Uterine cancers, including sarcomas of the endometrial stroma, were also elevated, but not to a statistically significant level.

Two government-sponsored chronic feeding studies have been reported, one in limited form by Calandra (1976) and later in more detail by Levinskas (1981). In this study Aroclor 1242, Aroclor 1254 or Aroclor 1260 at dietary levels of 1, 10 or 100 ppm was fed to groups of albino rats for two years. Table 5 lists the various liver lesions noted in the study. Changes attributable to the PCB exposure could be seen in groups exposed to each of the Aroclors at all exposure levels. However, no hepatocellular carcinomas were noted in the study.

A similar study was conducted by NCI (1978), in which Fischer 344 rats were fed 25, 50 or 100 ppm of Aroclor 1254 in their diet for 104-105 weeks. Table 6 lists the results. Again, altered foci were seen in all exposure groups. One and two hepatocellular carcinomas were seen, respectively, in the mid and high dose male groups and one in the low dose female group. However, the group incidences of these malignancies were not statistically different from that of controls, and it was concluded that Aroclor 1254 was not deemed to be carcinogenic in the bioassay. However, it should be noted that these two male groups had increased overall mortality rates compared with controls. Thus, fewer animals were at risk at older ages in the study. Based on a time course of hepatocellular carcinoma proportional to the fourth power of age, the expressed risk could have been reduced by as much as 40%. A

second finding of note was an elevation of lymphomas and leukemias among male rats (controls, 3/24; low-dose, 2/24; mid-dose, 5/24; high-dose, 9/24). None of the group incidences are significantly different from that of the control. However, the dose-related trend is significant at the p=0.04 level using the Cochran-Armitage test (Armitage, 1971) (not at the 0.009 level as suggested in the NCI paper). Most of the excess malignancies were lymphatic leukemias, although there were increases of granulocytic leukemia and various lymphomas in the two highest dose groups over that of controls. These were not significant, however. In the only other study to note the incidences of leukemias and lymphomas, Kimborough et al. (1975) did not observe a significant increase in lymphomas and leukemias (2 lymphomas and 0 leukemias in exposed animals vs. 0 lymphomas and 1 leukemia in controls) among female Sherman rats.

The results of a long-term chronic feeding study by Norback and Weltman (1985) are shown in Table 7. In this study female rats fed 100 ppm of Aroclor 1260 in their diet for 16 months and 50 ppm for an additional eight months showed a high incidence of adenocarcinoma and trabecular carcinoma in the liver. Ninety per cent of the animals had one or the other form of these hepatocellular carcinomas. In contrast, however, only four per cent of the male animals fed the same diet demonstrated such malignancies. This finding of a sex-related risk is similar to that of Kimura and Baba, noted above, and may be due to the competitive interactions of hormones.

Dogs

Neither hepatocellular carcinoma nor neoplastic nodules were found in groups of four male or female dogs fed 1, 10 or 100 ppm each of Aroclor 1242, 1254 or 1260 (Calandra, 1976). The only exposure-related finding was slight decreases in body weight gain in the high-exposed Aroclor 1254 and 1260 groups, as well as increases in liver weights and serum alkaline phosphatase levels in the groups exposed to 100 ppm of Aroclor 1260.

1.5 PROMOTION OF CARCINOGENESIS BY PCBS

The first study of the cancer-promoting effects of PCB s was that of Ito et al. (1973), who demonstrated that 250 ppm of Kanechlor 500, administered for 32 weeks with various concentrations of one of three isomers of benzene hexachloride, increased substantially the number of tumors over that produced by exposures to the benzene hydrochloride isomers alone. The results of this series of experiments is depicted in Table 8.

Nishizumi (1979) found that PCBs, PB and DDT administration after

an exposure to dimethylnitrosamine (DENA) in water at 50 ppm for two weeks enhanced the production of liver cancer. Table 9 lists the exposure regimens and the resulting outcomes, in terms of the number of observed liver tumors at 40 and 52 weeks. The greatest promoting activity was demonstrated by PCBs either alone or in combination with PB.

A study by Preston et al. (1981), confirmed the promotional effects of PCBs (Aroclor 1254) on DENA-induced tumorigenesis in Sprague-Dawley rats. Here, comparisons were made with PCBs especially purified of possible contamination by CDFs (to less than 100 ppb) and PCBs contaminated with CDFs (to 3 ppm). The results are shown in Table 10. While the CDF-contaminated PCBs were a slightly more effective promoting combination, the Aroclor 1254 alone quadrupled the number of hepatocellular carcinomas that developed.

Using an experimental cervical cancer model, Uchiyama and Chiba (1974) found no effect of dietary ingestion of 100 ppm of PCBs following implantation of a 3-MC impregnated thread within the cervix of rats. In contrast, an enhancement of the cervical cancer potential was demonstrated by the feeding of 100 ppm DDT for eight weeks.

In addition to promoting hepatocellular carcinoma, PCBs have been found to enhance the production of enzyme-altered foci in rat livers (Pereira et al., 1982). Rats were initiated by a dose of 0.3 mmol/kg body weight of DENA 24 hours after 2/3 partial hepatectomy. Aroclor 1254 was administered 7, 28 and 49 days after the DENA and some rats were sacrificed 21 days after each dose of Aroclor. The livers of rats that received Aroclor 1254 either 7 or 7 and 28 days following initiation contained a significantly increased number of GGTP foci compared to solvent controls. The number of foci in rats administered Aroclor 1254 on days 7, 28 and 49 was identical to the number in rats dosed once or twice with Aroclor. It was hypothesized that the Aroclor 1254 (and PB) appeared to decrease the time required for the appearance of GGTP-positive foci without altering the final number of such foci that developed.

1.6 PCB-ALTERED METABOLISM OF CARCINOGENS

Separate from their role as a cancer promoter, PCBs can also affect carcinogenesis by altering the metabolism of subsequently applied carcinogenic agents, either by increasing the metabolism of a carcinogen requiring activation or reducing a direct-acting carcinogen's effectiveness by enzyme-mediated deactivation. Deml et al. (1983), have demonstrated enhancement of carcinogenesis by the prior treatment with PCBs of benzo(a)pyrene (BAP)-initiated enzyme-altered foci. Here, prior administration of PCBs, which strongly induce aryl hydrocarbon hydroxylase, increased the number of altered foci by two orders of magnitude compared to application

of BAP alone. Additionally, subsequent applications of PCBs demonstrated a promotional effect by increasing altered foci by an additional factor of three over a regimen with discontinued PCB treatment.

Inhibition of carcinogenesis was demonstrated by Makiura et al. (1974) who showed that co-administration of PCBs reduced the number of liver lesions produced by the carcinogens, 3'-methyl-4-dimethylaminoazobenzene, N-2-fluorenylacetamide and/or DENA. The results are described in Table 11. The authors suggested that PCBs were strong inducers of the enzymes that metabolized the carcinogens to chemicals of lesser toxicity.

Similar inhibition of carcinogenesis has been found in offspring exposed to PCBs in utero and via mothers milk after birth (Nishizumi, 1980). Here, Wistar rats fed 50 ppm of DENA for five weeks had significantly fewer liver tumors than offspring of mothers unexposed during pregnancy.

In a test of the role of PCBs in a two-stage mouse skin tumorigenesis assay, it was found that neither PCBs, TCDD nor polybrominated biphenyls promoted skin tumors initiated by 7,12-dimethylbenz(a)anthracene (DMBA) (Berry et al., 1979). In contrast, PCBs and especially TCDD inhibited the formation of skin papillomas when applied for various periods prior to administration of the DMBA-phorbol ester regimen.

1.7 SUMMARY OF ANIMAL STUDIES

All chronic animal studies, with the exception of that of dogs, have demonstrated that PCB exposure produces precancerous lesions (neoplastic nodules or altered foci). These lesions have been produced in some exposure circumstances by PCBs of the most commonly used chlorinations (40% to 60%). The incidence of the various lesions, however, is strongly correlated to the degree of chlorination, the higher chlorinated PCBs producing the greater effect. These findings are not the result of a small contamination of the PCBs by CDFs; specially purified material showed virtually the same effect as material with a few ppm of CDF. While detailed studies have not been made of the relationship between the presence of PCB induced lesions and hepatocellular carcinoma, studies of the development of hepatocellular carcinoma in other animal studies would suggest that they are precursor lesions. The probability that cancer will develop from such lesions, considering that there is a continued body burden of PCBs in exposed animals, has not been studied. High incidences of hepatocellular carcinoma were found in two studies in which Aroclor 1260 was fed to rats for over one year. Kanechlor 500 was also shown to produce hepatocellular carcinomas in mice and a study in rats with Aroclor 1254 was marginally positive. All of the negative chronic carcinogenesis studies,

with one exception, were of durations less than one year and utilized relatively few animals, limiting the relevance of the results. Further, limitations in terms of intensity of exposure may have precluded the development of hepatocellular carcinoma in studies of low chlorination PCBs. Again, as with the development of neoplastic lesions, the higher chlorinated compounds were the most carcinogenic for a given exposure. In addition to hepatocellular carcinoma, PCBs were also found to produce a statistically significant increase in lymphomas and leukemias, based on an exposure related trend. No significant increase was observed in the one other study that noted the incidences of leukemias and lymphomas. PCBs were also shown to greatly enhance the effect of some initiating carcinogens, when administered subsequently. The evidence that PCBs are animal carcinogens is strong and unequivocal. The primary mode of action would appear to be that of a promoting agent. However, their action need not involve the prior administration of initiating carcinogens; cells altered spontaneously or by endogenous factors are capable of transformation into carcinomas by PCBs.

In addition to promotional activity, particularly in the liver, PCBs can alter the metabolism of other carcinogens, if administered previously. Here, their action can either increase or decrease cancer incidence, depending upon whether a carcinogen is activated or deactivated. Based upon known metabolism of a particular carcinogen, one could make prediction as to the effect of prior administration of PCBs. However, no data exist as to the effect of PCB exposure to humans early in life when its effect would be greatest.

SECTION 2

HUMAN MORBIDITY STUDIES

2.1 INTRODUCTION

Chloracne was associated with PCB exposure as early as 1954 (Meigs and Albom, 1954), but substantial concern for potential human health effects from occupational and environmental exposures to PCBs did not develop until severe clinical abnormalities were found among individuals who ingested PCB contaminated rice oil in Japan during 1968 (Kuratsune et al., (1972)). Approximately 1800 individuals have now been identified as having been exposed during this accidental poisoning episode. The clinical manifestations were given the name "Yusho", the Japanese word for "oil disease". (A similar incident occurred eleven years later in Taiwan, the disease from which was given the name "Yu Cheng".) While the Yusho symptoms were initially ascribed to PCBs, it was soon established that, in addition to PCBs, the oil was contaminated with substantial quantities of CDFs and polychlorinated quaterphenyls. Nevertheless, because of the severity of the Yusho symptoms, numerous epidemiological studies were initiated to obtain data on the mortality and morbidity of workers exposed to high concentrations of PCBs. As information has developed, it is now clear that the majority of the Yusho-Yu Cheng symptoms can be attributed to the other compounds, most probably the CDFs. This review will focus largely on the results of the PCB morbidity studies. However, because of the similarity of effects of PCBs and CDFs in animals, it is worthwhile to consider briefly the Yusho incident to obtain guidance in evaluating the human morbidity from relatively pure PCB exposures. In doing so it is important to remember that the toxic action of tetrachlorodibenzofuran is 500 to 2000 times greater per unit exposure than that of commercial PCB mixtures (See Table 1).

2.2 YUSHO DISEASE

The principal manifestations of Yusho were a variety of lesions of the skin and mucous membranes. Black comedos, acneform eruptions, pigmentation of the face, eyelids, gingiva and nails, and hypersecretion of the Meibomian glands were commonly found. As time progressed these symptoms diminished somewhat, but systemic disorders such as headache, gastric problems, joint swelling and pain, numbness of extremities and bronchitis-like symptoms developed in some of the individuals. Women experienced irregular menstrual cycles and weights of children born of exposed mothers were less than normal. Further, the children had retarded growth, abnormal tooth development, and some showed pigmentation characteristic of the exposure. Blood chemistries of exposed

individuals revealed increased levels of triglycerides and decreased bilirubin. While jaundice was initially reported as a subjective symptom, no later reference to it has been made. These findings and the relative absence of alterations of the concentrations of enzymes reflecting liver function in the serum would suggest that hepatocellular injury (separate from an increased cancer risk) was not a major factor in patients with Yusho disease (Kuratsune et al., 1972; 1976: Masuda, 1985). The above findings cannot be attributed to the Yusho patients' PCB exposure. Their PCB serum concentrations were much less than those of individuals heavily exposed to PCBs occupationally in whom most of the above symptoms were absent (Kuratsune et al., 1976).

2.3 PCB EFFECTS ON THE SKIN AND OTHER CUTANEOUS TISSUES

Skin lesions have long been associated with exposures to chlorinated aromatic hydrocarbons, especially the chlorinated naphthalenes. (See Taylor, 1974 and 1979 for a review of environmental chloracne.) One of the first outbreaks of chloracne associated with PCB exposure was reported by Meigs and Albom (1954) who described the development of chloracne in seven of 14 workers exposed to PCBs (and perhaps some CDFs as well) from a heat exchanger leak.

In one of the first cross-sectional clinical studies of heavily exposed occupational groups, Fischbein et al. (1979; 1982) identified skin lesions as the dominant abnormalities associated with PCB exposure. A history of skin rashes was reported by 39 % of an examined population (326 male and female capacitor manufacturing employees) and burning sensations by 25 %. Development of acne following employment was reported by 11 % of workers. Hyperpigmentation, thickening of the skin, and nail discoloration were each reported by approximately 3 % of the population. Thirty-seven percent of the examined individuals were found to have current skin abnormalities with the probability of occurrence correlating with serum PCB concentrations at a statistically significant level. The most commonly found abnormalities were erythema, swelling, dryness and thickening. Sixteen individuals (5 %) were found to have acneform eruptions and 48 (15 %) showed conjunctival and palpebral abnormalities characteristic of PCB effects.

Other investigators have reported similar abnormalities among other groups exposed to PCBs. Ten cases of acne and/or folliculitis and five cases of dermatitis occurred among 80 capacitor manufacturing workers examined in Italy by Maroni et al. (1981a; 1981b). They also noted two cases of bleeding hemangiomas; however, one had existed since birth but began to bleed

following employment. The second was in an individual who also developed leukemia. The man had been employed for 16 years since the age of 30. All of the workers with chloracne were employed in high exposure jobs. Their blood PCB concentrations ranged from 300 to 500 ppb.

In an examination of individuals having a somewhat lower exposure than those in the two previous groups, Smith et al. (1982) reported correlations of mucous membrane and skin irritation with serum PCB levels. However, no clinical abnormalities attributable to PCB exposures were observed. Other reports of chloracne among capacitor manufacturing workers include those of Ouw (1976) and Baker et al. (1980).

Another study of a relatively low exposure group (only 28 of 176 individuals had serum PCB concentrations in excess of 20 ppb) by Nethercott and Holness (1986) showed 22% of the study population to have various skin disorders on physical examination. No difference, however, was found in the frequency of such disorders between the high and low exposed groups. No definite case of chloracne was identified. One notable finding of the study was the reports of eight individuals that previously had skin cancer.

2.4 PCB ALTERATIONS OF BLOOD CHEMISTRY

Several studies have been conducted of groups of workers exposed to various concentrations of PCBs in which serum blood analyses were obtained. The results of these various studies are summarized in Table 12 which indicates whether there was any statistically positive association of particular liver enzyme with serum PCB concentration. Most of the results are negative and, when positive, the effect is relatively minor. Nevertheless, in considering the overall results, SGOT and GGTP, particularly, are increased with exposure to PCBs. The clinical significance of these findings, however, is uncertain.

Table 13 lists the association of serum lipid concentration with serum PCB level. Statistically significant increases in triglycerides and total cholesterol were associated in some studies with increased serum PCB concentrations. However, some studies did not fully control for body mass and the associated increase in serum lipids. Baker et al. (1980) and Smith et al. (1982) also noted an association of decreased high density lipoproteins with PCB concentrations. The possible clinical significance of these findings is uncertain, but the association of increased triglycerides and decreased high density lipids with an increased risk of coronary artery disease must be considered.

One of the dramatic features of animal studies is the increase in the induction of P-450 enzymes in the livers of rodents exposed to

PCBs. P-450a and P-450c levels are increased substantially in animals following administration of highly chlorinated PCBs. However, only limited human data exist. Alvarez et al. (1977) measured antipyrine clearance in five PCB exposed capacitor manufacturing workers and found that the antipyrine half life decreased significantly (from 15.6 to 10.5 hours). A slightly smaller effect was found among transformer repairers by Emmett (1985). As the potential consequences of this effect may be considerable, it is unfortunate that the data are so scanty.

2.5 LIVER ABNORMALITIES

The above mentioned increases in the serum concentrations of liver enzymes indicate a PCB effect on the liver. However, the clinical consequences of the findings are uncertain. Of greater concern is the report by Maroni et al. (1981b) of hepatomegaly in 14 of 80 examined individuals. None had a history of excess alcohol or drug intake. In addition to the examination findings, increased concentrations of GGTP, serum ornithin-carbamoyl transferase and serum alanine aminotransferase (SGPT) were commonly noted among those with enlarged livers.

Other clinical studies have not reported liver disease of such severity, if at all. For example, Fischbein et al. (1979) found only four individuals with significantly enlarged livers among 326 examined capacitor manufacturing workers. Further, two were in individuals with a high alcohol intake. Liver enlargement was found in only 3% of the study population of Nethercott and Holness, but the group exposure was relatively low.

2.6 PCB ASSOCIATED CARDIOVASCULAR EFFECTS

The occasional finding of serum lipid abnormalities suggests the possibility of a relationship between PCB exposure and cardiovascular disease. Of the various studies of groups occupationally exposed to PCBs, only one (Smith et al., 1982) mentions the results of an analysis to determine the correlation between serum PCBs and increased blood pressure. There an apparent correlation was found to be due to the confounding factors of age and sex.

Analyses of health data from community groups exposed to relatively high concentrations of PCBs have shown associations of elevated blood pressure with increased serum PCB concentration. The first such study (Kreiss et al., 1981b) considered data from a group that had high levels of serum PCBs from ingestion of fish. A correlation was found between serum PCB concentration and elevated blood pressure, particularly diastolic, increased GGTP concentration and serum cholesterol level. When the influence of possible confounding factors, including age, sex and body mass,

was removed, the statistically significant correlation with serum lipids no longer obtained, but the association of PCBs with elevated blood pressure remained. The significance of this finding in a study of general population members, considering their relative low exposure level (17.2 ppb, range 3.2-158) is uncertain. Stehr-Green et al. (1986) found a statistically significant association of high blood pressure with serum PCB concentration in a study of residents near three chemical waste sites. The association decreased to a non-significant level (P = 0.08) when age and smoking were controlled for. The confounding factor of obesity was not considered.

2.7 PCB RESPIRATORY EFFECTS

Two studies have been reported of spirometric values measured in individuals exposed to PCBs during capacitor production in the same facility. One by Warshaw et al. (1979) found a substantial prevalence of reduced forced vital capacity (FVC), both among smokers and non-smokers. Decreased FVCs were present in 14.9 % of males and 13.1 % of females tested using normal prediction equations developed by Morris et al. (1971). Exposure to pneumoconiosis producing dust could not account for these findings; the prevalence of x-ray abnormalities among the workers was extremely low. The lung function results of the workers studied by Nethercott and Holness (1986) were within the normal range.

The above results were initially confirmed by a study of the same population conducted by the medical staff of the company. However, in a later study (Lawton et al., 1986), it was found that their reduced FVC results were probably the result of technician inexperience and inadequate expiratory efforts on the part of those studied. The later Lawton et al. analysis indicated a 2.9 % prevalence of restrictive pulmonary dysfunction compared to 16.2 % prevalence in their earlier study. Prediction equations of Knudson et al. (1976) were used. The reason for the difference in the two studies of roughly the same population could lie in the use of the different prediction equations. Those of Morris et al. predict 5 to 10 % higher FVC values in adults than those of Knudson et al. Alternatively, the Warshaw et al. study could have been affected by technical flaws: it was conducted prior to the establishment of current strict standards for the conduct of pulmonary function tests (Morris et al., 1984). As with the possible association of increased blood pressure with serum PCB concentration, the single study indicating decreased FVC among PCB exposed workers must be confirmed in other populations.

2.8 REPRODUCTIVE EFFECTS

One of the significant results of PCB exposure to animals has been the pregnancy loss found in a study of monkeys (Allen et al.,

1979). In two groups of eight impregnated monkeys, five normal births occurred among those exposed to 2.5 ppm of Aroclor 1248 (in their diet for seven months) and one in those exposed to 5 ppm. Spontaneous abortions accounted for three pregnancy losses in the lower exposed group and four in the higher. At 5 ppm one stillbirth occurred and two animals failed to conceive. The significance of these monkey studies is enhanced by the finding of substantial reproductive problems among Yusho mothers (Kuratsune et al., 1972). Two stillbirths occurred among 13 pregnancies and reduced birth weight was common.

Few studies exist of human reproductive effects from pure PCB exposure. One by Fein et al. (1984) compared 242 infants of mothers who consumed PCB contaminated fish with 71 infants whose mothers did not. The results of the analysis indicated that exposed infants were 160 to 190 grams lighter than controls and their head diameter, 0.6 to 0.7 cm smaller. Analysis of covariance showed that none of these effects were attributable to any of 37 potential confounding variables. However, the analysis utilized only t tests or chi-square tests on dichotomized variables. Multiple regression analyses were not undertaken.

A second study evaluating birth outcomes of women exposed to PCBs was that of the New York State Department of Health (Taylor et al., 1984). An analysis of 51 births to women employed in high exposure areas of two capacitor manufacturing facilities showed the infants had lower birth weights than 337 infants born to women who worked in low exposure areas. The observed birth rate difference between the lower and higher exposure group was attributed to a shortened gestation period rather than to retardation of interuterine growth.

2.9 CANCER MORBIDITY

Only one study reported on the cancer history of the study group. Among the workers studied by Nethercott and Holness, eight workers reported a history of skin cancer and two of chronic leukemia (one lymphocytic and one myelogenous). Others reported cancers of the prostate, colon, larynx, and testicle, respectively.

2.10 OTHER EFFECTS

Immune dysfunction (Bekesi et al., 1983; Cheng et al., 1981) and hepatic porphyria (Strik et al., 1979; Chang et al. 1980) have been associated with environmental exposure to polybrominated biphenyls and among Yusho or Yu Cheng patients. However, porphyria was not found to be present in the populations studied by Smith et al.; no data have been reported on the immune status of populations exposed to commercial PCBs.

2.11 SUMMARY

The predominant finding among individuals exposed occupationally to PCBs is an increased prevalence of abnormal dermatological symptoms. Acneform eruptions, folliculitis and possible skin thickening may result from high exposures to PCBs, particularly of the higher chlorinated isomers. Commonly reported symptoms from PCB exposure are burning sensations in the eyes or skin and rashes. The rashes and burning sensations disappear after cessation of exposure, but some skin lesions may persist for years. Other consistent findings include elevation of various liver enzymes, particulary GGTP and SGOT, and serum triglyceride and cholesterol concentrations. Liver enzyme induction has also been documented, which may account for the commonly found elevated GGTP concentrations. Some workers in one examined group were found to have varying degrees of hepatomegaly. However, this has not been a consistent finding among other populations exposed occupationally to high concentrations of PCBs. Studies among exposed individuals in the general population suggest the possible association of increased diastolic blood pressure with increased serum PCB level. One study of workers associated a reduced forced vital capacity with PCB exposure. However, these last two findings require confirmation in other studies. Two limited studies suggested that infants born of mothers exposed to PCBs were smaller. A possible causal factor in both the lower birth weights and head sizes was a shortened gestation period associated with increased serum PCB level.

2.12 PCB STUDY DESIGNS

The evidence is clear that occupational exposure to high concentrations of PCBs can result in a variety of skin lesions. These can occur from relatively short exposures and persist long after exposure ceases. Also established is the association of increased serum concentrations of the liver enzymes, SGOT and GGTP. Less well established are associations of PCB exposure with increased serum concentrations of cholesterol, triglycerides and high or low density lipoproteins. Here, because of the high lipid solubility of PCBs and their storage in fat tissue, extremely careful multiple regression analyses must be performed to separate out the confounding factor of body lipid mass. Similarly, careful analyses are necessary to confirm observed associations of increased blood pressure with serum PCB level. Also uncertain, because of the paucity of studies, are the suggestive associations of reduced birth weight and size with serum PCB levels or degree of occupational exposure and the possible association of reduced FVC with occupational PCB exposure. Nothing is known concerning the effect of PCBs on human immune function.

Clinical examinations of PCB exposed groups should include careful considerations of the following systems:

Dermatologic: The full spectrum of skin lesions should be documented. However, special attention should be paid to those characteristic of chloracne and those associated with PCB exposure. See, for example, Taylor (1974; 1979) for a review of environmental chloracne. Control populations must be included in any examinations because of the non specific nature of many of the PCB associated dermatologic findings.

Cardio-respiratory: Any examination should include three independent measures of blood pressure designed in a way to control for technician differences and patient anxiety. Analyses of spirometric data should be done using prediction equations of Morris et al. (1971) as modified by Miller et al. (1980) or those of Miller (1986).

Blood chemistries: These should be overnight fasting samples. Consideration might be given to sending duplicate samples to the laboratory to obtain a measure of their analytical variability. PCB analysis should follow the technique suggested by Burse et al. (1983a). See also Burse et al. (1983b) for an assessment of interlaboratory variability.

Immune: Both humeral and cellular immune function should be determined. Some guidance in determining possible effects can be gained from studies of populations exposed to polybrominated biphenyls (Bekesi et al., 1978; 1983).

Reproductive: One of the most worrisome areas about which we have inadequate information is the effect of PCBs on female reproduction. Animal effects were dramatic (Allen et al., 1979) and human effects were suggested to occur from non-occupational exposures (Fein et al., 1984). Any examination of exposed workers should certainly include a reproductive questionnaire. The results, however, being based on recall over many years, are likely to be very uncertain. To be meaningful, a reproductive study should be prospective and would require the enrollment of a large population. However, some recently developed techniques provide a very early identification of pregnancy. Their use indicates that 30 % of

all pregnancies end in spontaneous abortion, half of which were unrecognized by the woman (Wilcox et al., 1985). This high percentage of background spontaneous abortions substantially increases the power of a prospective reproductive study. An enrolled group would provide a urine specimen at each menses. If the bleeding were the result of a spontaneous abortion, a high level of Human Chorionic Gonadotropin would be present in the urine. Later miscarriages and birth outcome would be determined in the standard way. Even with the greater sensitivity, the study would require at least 1000 person-years of follow-up (of exposed and control women attempting to become pregnant). It would also be very expensive.

The above comments are only indicative of some of the epidemiological considerations important in a study of PCB effects. Prior to the development of any study protocol, consultation with experts in a particular field would be necessary. It would also be important to involve such experts in determining whether a particular study is even warranted. Among the symptoms definitely associated with PCB exposure, it is unlikely that much additional information can be gained from a study of dermatological abnormalities. Industry exposures have decreased and symptoms among past heavily exposed workers are decreasing. Similarly, it is not very important that additional data on the serum enzymes be obtained, although more data on enzyme induction, as measured by drug clearance, would be useful. While our information is very uncertain, lack of evidence of substantial effects among workers relating to effects on the cardiac, respiratory or immune systems suggests that studies of these systems (including serum lipids) should be undertaken with a clear goal in mind and with specific scientific hypotheses. On the other hand, I think a study of reproductive effects is important, although it would be both expensive and difficult to conduct.

The use of PCBs in new electrical equipment is banned in the United States. The largest group currently exposed to PCBs is electrical equipment repair workers who maintain large electrical transformers and capacitors containing PCBs. These would largely be employees of electrical utility companies, although equipment manufacturers may employ a repair staff that works on old transformers. The best source of exposed populations would be among the above work groups. A group for the study of pregnancy outcome is much harder to obtain. Women exposed in the past to high concentrations for long periods of time are no longer

planning families. Some can be recruited among current and former workers in the electrical equipment manufacturing and using industry, but I think several regional studies would be required.

SECTION 3

HUMAN MORTALITY STUDIES

3.1 INTRODUCTION

Data are available from four research groups in three countries on the mortality experience of workers exposed to PCBs during the manufacturing of electrical capacitors (Brown et al., 1981; Brown, 1986; Bertazzi et al., 1982; Bertazzi et al., 1987; Gustavsson et al., 1987; Nicholson et al., 1987). The results of the studies were varied. Those of Brown et al. suggested an excess of liver and biliary tract cancer and possibly rectal cancer, while those of Bertazzi et al. suggested an excess of hematological neoplasms and gastro-intestinal cancer. The study of Gustavsson et al. had too few deaths to enable any conclusions to be drawn and that of Nicholson et al. was largely negative. The results of no one study were sufficiently definitive to allow a firm conclusion to be drawn regarding the human carcinogenicity of PCBs.

It is possible to combine the results of the four research groups from the publication data and data available in preprint form to provide stronger evidence for any relationship between cancer at some site and PCB exposure. However, any overall combined mortality estimate would necessarily have to utilize crude estimates of expected deaths for some sites of interest. Further, no data were available that would allow the combining of data according to exposure variables of interest such as duration from onset of exposure, duration of exposure and age at first exposure. In order to be able to combine data from the four studies more accurately and to take advantage of analyses by exposure and time variables of interest, the principal author of each study was asked if he wished to participate in a combined analysis of all available PCB mortality data. Each responded positively and either sent basic cohort data or performed analyses according to particular time and exposure variables.

The purpose of this chapter is to review the available data on the exposure circumstances of the study populations, the mortality experiences of the study groups, both as published, as in preprint form or as supplemented by further data submission for this analysis. With these additional data, advantage can be taken of currently accepted models for the age, dose and time dependence of exposure related cancers to focus on time and exposure periods of most relevance for the cancer sites of interest. Analyses will be performed that will provide information on the strength of the evidence for human carcinogenicity from PCB exposures that will be based on all data available in the above studies.

3.2 INDUSTRIAL HYGIENE MEASUREMENTS AND POPULATION EXPOSURE ESTIMATES

The study cohorts came from five different company facilities, some involving separate plants for heavy and light duty capacitor manufacturing. The facilities studied by Brown et al. were those of two different electrical equipment manufacturers, one with a plant located in southeastern Massachusetts and one with two plant facilities located in upstate New York. The population of Nicholson et al. also came from the New York plants, although their cohort was defined differently from that of Brown et al. (Cohort members present in both study groups have been identified and eliminated from the group of Nicholson et al. in the following analysis.) The plant studied by Bertazzi et al. was located north of Milan, Italy and that of Gustavsson in Stockholm, Sweden.

From the published descriptions, the work activities in each facility appeared to be similar. Typical processes during the manufacturing of large industrial capacitors involved the forming of "capacitor packs" consisting of rolls of paper, film and foil which were covered with cardboard and bound. These were tested for electrical quality, inserted into metal capacitor boxes and leads connected to the outside. Following assembly the capacitors were filled with PCBs. While this was done in later years utilizing automated equipment, flood filling chambers were utilized often in the process. Once filled, the capacitors were placed in a vacuum to remove any moisture and the filling holes sealed by soldering. The finished capacitors were tested and, if satisfactory, cleaned with a solvent, usually trichloroethylene. Capacitors were then painted, dried and packed for shipping. Capacitors that failed the electrical tests were sent to a salvage operation where the reusable components were removed and the capacitors reconstructed as appropriate.

The smaller electrical capacitors, such as those used in household lighting fixtures or appliances, were also constructed by forming rolls of paper, film and foil which were inserted into cases. Capacitors were filled with dielectric fluids in open baths, placed under vacuum and sealed by either crimping or soldering. After washing with phosphates, trichloroethylene or other solvent, the capacitors were tested and packed for shipping.

Obviously, during the open filling operations of either small or large capacitors, the air exposures above the PCB baths would be close to the vapor pressure of the PCBs. In the bath filling operation of one facility workers walked on slatted wooden floors to prevent slipping on pools of PCBs spilled onto flat concrete surfaces. In addition, the opportunity for skin contact was extremely high. Although workers usually wore rubber boots and rubberized clothing in high contact areas to protect themselves, protective clothing may not have been adequate. Dispersal of the PCBs onto workplace surfaces was common. Surface contamination as

high as 0.159 mg/cm^2 was measured in the Italian plant during 1977; levels as high as 0.006 mg/cm2 were measured in 1982, two years after the cessation of PCB use. To the extent that air from the filling, sealing, or salvage operations was carried to other parts of a manufacturing facility, widespread exposure occurred. The degree of exposure, of course, depended on the circumstances of the manufacturing plant.

Table 14 lists exposure measurements available from the five manufacturing facilities reviewed here. As can be seen in the high exposed areas, air concentrations approached 1 mg/m^3 and evidence for widespread dispersal into the case and component manufacturing areas was present. It should be emphasized that these measurements were made during the late 1970's, in some cases after installation of engineering controls and process alteration. For example, the NIOSH measurements in the Brown plant 1 were taken after the quantity of PCBs used in capacitors was reduced to 25% of that used previously and after installation of ventilation equipment. The improvement in air quality from these measures is seen in the difference between the NIOSH and earlier company measurements. While the industrial hygiene data that are available are extremely limited, they suggest that the time weighted average workplace air exposures of electrical capacitor manufacturing workers ranged from concentrations in excess of 1 mg/m^3 in the high exposure areas to general plant-wide concentrations of 0.05 to 0.1 mg/m^3. There is no evidence for substantially different airborne concentrations in the different plants here reviewed.

Dermal absorption also can be an important, and much more variable, route of body entry to PCBs. Observations on the potential for exposure of workmen during transformer maintenance by Lees et al. (1987) indicated numerous instances of dermal contact, whether by contact with PCB containing oil or PCB contaminated surfaces. The amount of dermal absorption was not estimated, but they point out that the absorption of one drop of PCB fluid (0.05 mL) would result in an intake of 54 mg of PCB. This is equivalent to the intake from an 8 hr. air exposure of 7 mg/m^3.

In addition to possibly different exposure conditions in the five facilities under review, the average exposure durations of the individuals in the several cohorts differed substantially because of different cohort entry criteria for duration of employment used by the various investigators. Table 15 lists descriptive information about each of the four groups for which epidemiological data are to be reviewed. Individual exposure information was unavailable for the members of any group, although Brown selected for observation only workers deemed to have higher exposures and Nicholson ranked individual workers by exposure estimates based on job title. For one cohort, even information on the jobs held by all cohort members was lacking. It would have been ideal to have

information on the work exposure of each cohort member. This would allow an analysis to be made according to both intensity and duration of exposure. Here, however, we can only utilize duration of exposure categories. Because of the different cohort definitions, equal durations of exposure do not correspond to equal cumulative exposure. The durations of work characterized by Brown et al. are likely to involve, on average, two to three times the intensity of exposure for the employment periods in the subcohort of Nicholson, since the duplicated members removed from the Nicholson et al. cohort were those with higher exposure. The intensities of exposure for the cohort members in the groups studied by Bertazzi et al. and by Gustavsson et al. are likely to have an intermediate exposure intensities on average.

3.3 REVIEW OF EPIDEMIOLOGICAL STUDIES

Tables 16 and 17 list the summary mortality results of each individual study, separately for males and females. The information listed in these tables is that provided for this review. For cancer mortality it is more extensive than that provided in the published studies or those in preprint form. Details relative to each separate study are provided below. For the sites originally considered in a given study, the expected and observed deaths are identical with those published for the studies of Brown (1986) and Gustavsson et al. (1986). The observed and expected deaths listed for Nicholson et al. are only for the subgroup in their cohort that was not also in the cohort of Plant 1 of Brown. The expected deaths for the Bertazzi cohort are those calculated using the rates of the region (Lombardy) in which the plant is located, rather than those of the local town or of the nation. These are deemed to best represent the rates for the study population. We are grateful for the extra effort by Dr. Bertazzi to make these calculations. In none of the individual cohorts was the number of deaths sufficient to allow meaningful analyses to be made with respect to exposure or time categories that might relate to cancer risk. Thus, only data on overall cohort cause specific mortality is presented in the tables.

Brown and Jones (1981); Brown (1986)

The first mortality study of workers exposed to PCB was that of Brown and Jones (1981) who published data from a retrospective cohort study of 2,567 workers in two production complexes using PCBs during the manufacture of electrical capacitors. The study cohort was defined as all workers who accumulated at least three months of employment at any time in areas of the plants where there was a potential exposure to PCBs, as designated by the company and confirmed by a NIOSH industrial hygiene survey. In the first follow-up of the group, the vital status of each individual was determined as of January 1, 1976. From 1940 through 1976, 160 individuals of both sexes had died compared to 182.35 expected. While the number of cancer deaths was less than

expected (39 obs. vs 43.79 exp.), excess mortality occurred for rectal cancer (4 obs. vs 1.19 exp.) and cancer of the liver, gallbladder and biliary passages (3 obs. vs 1.07 exp.). Most of the rectal cancers occurred among females employed in one of the plants, resulting in an excess for that plant that achieved statistical significance at the 95% level (3 obs. vs 0.50 exp.). In the case of the liver cancers, it was indicated in a follow-up study by Brown (1986) that one of the three cancers was metastatic from another site, thus, weakening the association based on death certification. Further, limited analyses according to time from onset of first exposure did not indicate any increasing risks with greater latencies.

The mortality experience of the above cohort was updated through 1982 by Brown (1986). During the additional seven years of follow-up, there were no additional deaths from cancer of the rectum and the original SMR of 346 decreased to 211. On the other hand, two additional deaths from cancer of the liver and biliary passages occurred, both among females. For the whole cohort, the SMR for liver and biliary tract cancer (ICD 155 and 156) was 210 if the above mentioned liver cancer that was metastatic is not included. If this cancer is included, the resulting SMR achieves statistical significance at the $p<0.05$ level using a one-sided test. (The argument for including it is that general population rates include some liver cancers that are improperly listed on the certificate of death and that one should compare like data.) Setting aside the argument for the moment, it must be recognized that only extremely high risks can be expected to achieve statistical significance if the cause of death is relatively rare. The finding of a more than twofold excess of cancer of the liver, gallbladder and biliary passages, while of marginal statistical significance, is strengthened by the much stronger animal data which indicate liver cancer, and perhaps also biliary tract cancer, to be a possible outcome from PCB exposure.

Brown used U. S. mortality rates to calculate the expected number of deaths. The liver and biliary tract cancer rates for whites in the counties in and about which the plants were located were both lower and higher than the U. S. rates (34% lower for males and 12% lower for females in the counties about the New York plant; 23% higher for males and 7% higher for females in the county in which the Massachusetts plant is located) (Mason et al., 1974). Further, individuals whose job titles indicated an exposure to trichloroethylene, a liver carcinogen in animals, were eliminated from the study cohort of Brown et al.. Thus, a consideration of possible epidemiological biases that might affect the results for liver and biliary tract cancer does not indicate any that would suggest a lower risk than that in Brown's paper (1986) and in Tables 16 and 17. On the other hand, the suggested elevated risk for cancer of the rectum is weakened by similar considerations. The local rectal cancer rates for both the New York and Massachusetts plants are significantly ($p<0.05$) higher than U. S.

rates (by 33% to 39%).

Gustavsson, Hogstedt and Rappe (1986)

A small group of 142 male Swedish capacitor manufacturing workers was followed from 1965 through 1982. Twenty-one deaths from all causes occurred, seven of which were from cancer. Among the cancer deaths two were of the lung and one of the ampulla of Vater (ICD 156) (Gustavsson, 1987). In addition one individual developed both a malignant lymphoma and a mesenchymal tumor. Analyses were conducted by job title and duration of exposure, but did not provide any information allowing an association to be made between the observed mortality and PCB exposure. The very few deaths limit the conclusions that can be drawn from this study. Swedish national rates were used for the calculation of expected deaths; these may underestimate the deaths to be expected in Stockholm (local rates may be available soon and the results of this study can be recalculated. However, the use of these rates will have only a trivial effect on the overall results of this review.)

Bertazzi et al. (1982), Bertazzi (1987)

In the initial study of Bertazzi et al. (1982), all production employees who accumulated at least six months of service in an electrical capacitor manufacturing facility between 1946 and 1970 were included in the study population. Mortality was observed from 1954 through 1978 and compared with that of the town in which the factory was located. Among male workers, eight malignancies were observed vs 3.3 expected (p=0.040). Cancer was also elevated among females (6 obs. vs 2.3 exp.). The greatest cancer excesses were of the lymphatic and hematopoietic system among both males and females and of digestive cancer among males.

The above cohort was expanded by adding non-production workers and including all individuals with at least one week of employment subsequent to 1946. The rationale for inclusion of short term workers was that chloracne cases were found among plant employees with fewer than six months of employment. While information on date of hire and residence was available, work histories were available only for workers hired subsequent to 1978.

The updated mortality experience compared the observed number of deaths by cause to those expected, based upon both national mortality rates and rates of the town in which the plant was located (population 150,000). Overall cancer and cancers of the lymphatic and hematopoietic system were elevated substantially for both men and women when compared with expected numbers of deaths calculated using national rates. Among the men, there was also a significant elevation of cancer of the gastro-intestinal tract.

Expected numbers of deaths also were calculated using local rates. These were similar to those calculated using national rates for males, but the number of female deaths was about 40% lower. Investigation of the significant difference between these expected numbers led to the conclusion that the expected rates for individuals under the age of 45 were potentially inaccurate because of the few deaths that occurred among individuals of such ages in the town (Bertazzi, 1987). As most of the females employed in the plant had yet to reach age 45, these rates unduly influence the overall expected mortality. A comparison of age standardized town rates with regional and national rates shows relatively close agreement. To avoid the inaccuracies associated with small numbers of deaths and to best reflect regional rates, expected numbers in Tables 16 and 17 were calculated using rates of the Lombardy region.

Among the various cancers, one leukemia among males and two lymphomas among women occurred within two years of first employment. It is unlikely that these three deaths can be associated with PCB exposure and later analysis will consider these deaths to be unrelated to employment. Of note, however, is the finding of a hepatocellular carcinoma and a cancer of the biliary tract. As with all studies having relatively few deaths, the results are only suggestive of possible risks.

Nicholson et al. (1987)

The final study available for analysis is that of Nicholson et al. (1987) who investigated the mortality experience of workers in one of the plants that was included in the study of Brown and Jones. The cohort, however, was defined differently and 521 of 769 individuals in the Nicholson et al. cohort were not included in the cohort of Brown (1986). The Nicholson et al. study population consisted of all individuals employed in either of two production facilities who achieved five years of service and whose employment began prior to 1954. In one plant PCBs were used since 1946 and in the other since 1951. Person-years-at-risk were accumulated from ten years after initial employment or initial use of PCBs within the particular facility. The data presented in Tables 16 and 17 only include that for the group of 521 not in the Brown group. Neither the overall results of the full study nor of the subgroup listed in Tables 16 and 17 indicate any cancer risks. Thirty-seven cancers were observed, whereas 38.3 were expected, based upon upstate New York mortality rates. Leukemias were in excess in the group listed in Tables 16 and 17 (4 observed vs. 1.28 expected: $p=0.041$) although not in the full cohort of 769. Another significant observation was that no cancer deaths occurred among males 30 or more years from onset of exposure, whereas 5.3 would have been expected (0 vs. 8.3 in the full Nicholson et al. cohort). Other than the above findings, site specific cancer mortality, according to various time and exposure strata did not indicate any PCB associated effect.

Bahn et al. (1976)

Two cases of malignant melanoma were reported among 31 men exposed to Aroclor 1254 in a refinery. While the excess is statistically significant ($p<0.001$), the individuals also were exposed to other chemicals within the refinery. Thus, without confirmation in other studies, an association of melanoma with PCB exposure cannot be made. Only one melanoma was identified in all cohorts of workers exposed to PCBs during capacitor manufacturing vs. 1.2 expected.

Kuratsune et al., (1986)

An abstract of the mortality experience of Japanese Yusho patients has been published. While any excess mortality cannot be attributed to PCBs because of the concomitant high DBF exposure, the spectrum of mortality is of interest because of the similarity of toxic action of PCBs and DBFs (Table 19). Among 1761 patients followed through 1983, 79 deaths occurred among males and 41 among females, compared, respectively, to 66.13 and 48.90 expected. Cancer deaths were significantly increased among males (33 obs. vs 15.51 exp.), but not among females (8 obs. vs 10.55 exp.) Nine male and two female deaths of liver cancer occurred. The expected numbers were, respectively, 1.61 and 0.66, using national rates and 2.34 and 0.79, using local rates. Additionally, eight lung cancer deaths occurred among males compared to 2.45 expected.

3.4 SUMMARY OF OVERALL EPIDEMIOLOGICAL STUDY RESULTS

A review of Tables 16 and 17 shows that each individual study, by itself, does not provide definitive information on cancer risk from exposure to PCBs. **Table** 18 combines the cancer results from the various studies and serves to indicate the sites for which further analyses are warranted. In considering the data of Table 18 it must be remembered that the cohorts from which the data came have different average durations and intensities of exposure. Further, in three of the cohorts, follow-up for some of the cohort members began within one year of first exposure to PCBs: in one a latency of ten years was utilized. It is also important to recall the conclusions of the various experimental animal studies when reviewing Table 18. There, very strong evidence from several studies demonstrated that PCBs induced liver cancer, probably as a promoter acting in concert with other carcinogenic agents or processes. One animal study demonstrated an increase in lymphomas and leukemias (NCI, 1978), although a second study (Kimbrough et al., 1975) did not show as clear an increase (2 lymphomas in the exposed group vs. 0 in the controls--0 leukemias in exposed animals vs. 1 in controls). No other animal study reported on the presence of leukemias or lymphomas; they may not have been investigated in studies focused on liver effects.

A review of the data in Table 18 shows that there is a statistically significant increase of cancer of the liver, biliary tract and gallbladder. Of the seven cancers, all appear to be primary; two are of the liver, four are of the extrahepatic biliary tract and one is of the gallbladder. The finding of a substantial number of preneoplastic lesions in the biliary tracts of rats fed Aroclor 1260 (Table 7) provides strong support for combining the results of the liver and biliary tract. If one considers the results for the biliary tract and gallbladder alone, the excess for those sites is also significant ($p<0.05$). All of these cancers occurred after ten years from onset of employment in a PCB using facility. The age, time and exposure dependence of these malignancies will be considered in more detail below.

The other sites for PCB related cancer suggested by the animal studies are the lymphomas and leukemias. Both of these sites are in excess, but not at the 0.05 level of significance. Of the 19 leukemias and lymphomas, two lymphomas and one leukemia occurred in individuals within two years of employment; one additional lymphoma occurred within five years of employment. It is unlikely that these four malignancies can be associated with plant employment, absent particularly bizarre exposure circumstances. Nevertheless, because of the elevated risk and the presence of increased lymphomas and leukemias in one animal study, it is appropriate to consider the mortality at these sites in more detail (see below).

Other sites that are elevated, but not at a statistically significant level, include rectal cancer and cancer of the kidney and urinary bladder combined. Neither of the two long term animal studies that considered all malignancies suggest these sites to be in excess. Interestingly, a motivation for the Kimbrough et al. (1975) study was the finding of a urinary bladder cancer in a group of ten rats exposed in a pilot experiment. Further, these sites are on major excretory pathways for PCBs and their metabolites. Nevertheless, the current data are insufficient to allow a statement to be made with respect to human carcinogenicity at these sites and the small number of excess cancers do not warrant further consideration at this time. There was no evidence for an excess of skin cancer suggested by the morbidity study of Nethercott and Holness (1986).

Later in this review a more detailed analysis will be undertaken of the cancers of the liver and biliary tract and of the lymphatic and hematopoietic system because of the relatively high risks shown in Table 18 and the presence of corroborative animal data. Further, this later analysis will consider whether there is any evidence in these studies that PCBs may affect human cancer risk through the stimulation of liver enzymes that would alter the metabolism of other carcinogenic species to which individuals may

be exposed. Prior to doing so, it is necessary to consider some aspects of the time course of human cancer risk in order that we may identify the age, time and exposure categories of most importance for PCB related cancer risk.

3.5 TIME COURSE OF HUMAN CANCER

Promotional effects

As indicated in animal studies and suggested by human studies, PCBs may act as promoters of liver cancer. Here their role would be to increase the incidence of such cancers by promoting cancer in cells which have been initiated by exposure to other carcinogens or altered spontaneously by endogenous factors. The effect is likely to be greatest for hepatocellular carcinoma, but other sites must not be excluded from consideration, based upon the finding of excess lung cancer among individuals exposed to PCBs and DBFs in Japan.

The animal data do not provide information on what would be the time course of risk of promotional effects from exposures to PCBs. One might hypothesize, however, that the risk would be related to the body burden of the highly chlorinated PCBs. Some information on the persistence of various PCB isomers in humans exist. Wolff (1987) has measured relative serum PCBs concentrations in the same individuals collected in two examinations held 45 months apart. The data (Table 20) suggest that PCB isomers are cleared with half-lives of from two to 20 years. However, the data are uncertain because of the difficulty in estimating the GC-MS peak heights for some isomers and the possible improvement in sample preparation over the intervening time periods. Limited data, published by Bertazzi et al. (1987), indicate a decrease in average serum PCB content from 283 ppb to 203 ppb in 37 workers over a period of five years for isomers characteristic of Aroclor 1254. This suggests a half-life of 10.4 years.

Based upon the assumption of first order kinetics for the removal of PCBs, it would be expected that the adipose tissue concentrations would be represented by the equation:

$$C_p = K_p(1-e^{-bt}) \qquad (1)$$

where C_p is the adipose tissue concentration of a particular PCB isomer, t the time from onset of exposure to a constant level of PCB, b a characteristic time constant equal to $0.693/T_{1/2}$ and K_p a constant for the particular isomer. Serum concentrations, being in equilibrium with those of adipose tissue, would be expected to follow a similar time course. Following cessation of exposure it is expected that the concentration would decay according to the relationship:

$$C_p = C_{pmax}e^{-bt} \qquad (2)$$

Using a model in which the promotional effect of PCBs is assumed to be proportional to the body burden five years previously, it is possible to calculate hypothetical relative risks in order to illustrate the time and exposure categories that would most accurately express the risk. Such a calculation is shown in Table 21, which depicts hypothetical risks according to duration and time from onset of exposure to PCBs. Figure 1 shows representative hypothetical body burdens of PCB according to the model described by Equations 1 and 2. The chosen exposure circumstance is one that would express a maximum relative risk of 2.0 from infinite duration exposure. In the calculation, a PCB half-life of 10 years was used. Clearly, the more important time periods for examination are those ten or more years from onset of employment and within 15 years of cessation of exposure.

The above example assumed that the population under observation had a uniform exposure to PCBs during the course of employment. Exposures of different and varying intensities can be considered by calculating a yearly relative PCB risk for each individual, according to the above model, and accumulating expected deaths for the population, person by person, in cells categorized by relative PCB risk.

Initiation effects

As described earlier, it is possible that PCBs might also enhance or diminish the effect of initiating carcinogens by virtue of increasing the metabolism of these agents in the liver through the stimulation of liver enzymes. On the one hand, carcinogens that an individual would be exposed to otherwise could be more readily detoxified. On the other hand, carcinogens requiring activation could be increased in potency by virtue of more rapid metabolism to the active species. The multistage model of carcinogenesis predicts that the effect of initiating carcinogens that later are promoted by a constant background of endogenous carcinogens or other factors, would follow the relationship:

$$I = At^k \qquad (3)$$

where I is the incidence of cancer induced by the initiating agent, and t the time from onset of exposure. A and k are empirically derived constants. Typical values for k lie between 3 and 6. A delay in the expression of the risk can be incorporated in the equation in which case the incidence would be proportional to $(t-d)^k$. In this case, however, the value of k would be less. At times 20 years from onset of exposure, either expression, with the appropriate constants, could be used to match any available data. Considering an exposure of duration d to PCBs leads to the following expression for cancer incidence (no delay considered):

$$I = (A/(k + 1))(t^{k+1} - (t - d)^{k+1}) \qquad (4)$$

Equation 4 depends only on duration and time from onset of exposure and is independent of the age of the individuals or the underlying risk of cancer in the absence of exposure.

Inasmuch as the underlying risk of most cancers increases as a power function of age, the ratios of incidences calculated by the above equation to the underlying risks (SMRs) would be substantially different for individuals exposed early in life compared to those exposed later in life (at equal times from onset of exposure). Thus, initiation effects of PCBs may be revealed by analysis according to age of first exposure. If the effect of an agent is to decrease the number of initiated cells that would occur otherwise, then Equation 4 would reflect the reduction in cancer risk. The effect of such alterations in cancer risk by PCBs is shown in Figure 2 schematically for individuals first exposed at two different ages (20 and 40 years). A hypothetical constant excess number of cases ($200/10^6$ person-years) is assumed to develop from an increased effect on cancer initiation. However, because of the steeply rising underlying risk, the SMRs at 20 years from onset of exposure differ greatly for the two exposure groups.

While the PCBs have their principal effect in the activation of liver enzymes, the carcinogens acted upon by these enzymes might play a role in the induction of cancer at any site within the body. Thus, observation of total cancer mortality and cancer mortality of the most common sites will be considered in an attempt to identify any PCB effects on cancer initiation.

3.6 AGE, TIME AND EXPOSURE DEPENDENCE OF POSSIBLE PCB RELATED MALIGNANCIES

The combined mortality experience of all the study cohorts that was reviewed above suggested cancers of the liver, biliary passages and gallbladder and cancers of the lymphatic and hematopoietic system as possibly being related to PCB exposure. In this section we will consider the evidence for an association at these sites in more detail. In doing so it is useful to consider criteria that Sir Austin Bradford Hill (1977) suggested should be utilized by epidemiologists when considering whether human disease can be related to a specific exposure circumstance. These criteria are:

1. Strength of the association: Is the effect under consideration a marginal one showing an increased risk that is not statistically significant or is the evidence of a substantial nature?

2. Consistency: How many studies demonstrate the effect in

question and are the results comparable?

3. Specificity: Is the action of the agent specific and does it act similarly in different exposure circumstances?

4. Time relationships: Is the time course of the disease related to the exposure circumstances?

5. Dose-response relationships: Is there an increasing risk commensurate with an increasing exposure?

6. Biological plausibility and coherence of the evidence: Do animal data support the human epidemiological evidence and is any proposed mechanism of action a plausible one?

7. Effect of removal from exposure: Does a reduction in the exposure lead to a reduction in risk in individuals experiencing improved circumstances?

8. Support from analogous experience: Do similar chemicals act similarly?

Unequivocally positive answers to each of the above questions are rarely obtainable in most occupational exposure circumstances and no epidemiologist nor regulator would require that all be answered positively before reaching a conclusion on causation. In practical situations, one considers the overall evidence, recognizing that there are limitations in many human epidemiological studies that prevent all of the criteria from being adequately addressed. Let us consider the evidence for the relationship between PCB exposure and cancers of the liver, biliary tract and gallbladder and for lymphatic and hematopoietic cancers.

Liver, biliary tract and gallbladder cancer

Table 22 lists the cancers in all studies that were certified on death certificates as of the liver, biliary tract or gallbladder. With the exception of the female deceased in 1979, all would appear to be primary malignancies; pathological confirmation is available for five. All occurred ten or more years from first employment in plants using PCBs among workers who were first employed between 1949 and 1960, periods when exposures to PCBs may have been very high. The cancers were largely of the bile ducts and, with two exceptions, extrahepatic.

An excess of liver lesions, including hepatocellular carcinoma, was the most common positive finding in animal studies. High incidences of liver cancer were found in two studies of rats fed Aroclor 1260 for over one year. Lesser risks were found among mice fed Kanechlor 500 and rats fed Aroclor 1254. Biliary passages also were one of the sites of PCB action in animals.

Norback and Weltman (1982) found a substantially increased number of cholangiomas along with the presence of cholangiofibrosis in rats exposed to Aroclor 1254. Ito found bile duct proliferation to be present in all rats fed 100 to 1000 ppm Kanechlor 300, 400 or 500 and mice fed 250 and 500 ppm Kanechlor 400 or 500. Further, some of the hepatic carcinomas observed by Norback and Weltman displayed a ductal pattern. The close association of hepatocyte-like cells and ductal-type cells in the adenocarcinomas suggested a common origin of the cells. Thus, the animal data suggest that both the liver and the biliary passages may be sites of PCB related cancers in humans. Because of their interrelatedness, it is appropriate to consider them together. However, as mentioned above, in human studies the excess risks for cancer of the biliary tract and gallbladder are as elevated as that of the liver and biliary tract combined.

Table 23 lists the expected and observed number of deaths in all of the cohorts under review by years of exposure and years since onset of employment. The metastatic cancer of the Brown et al. cohort is excluded. The expected deaths were calculated using local or national rates for primary cancer of the liver, biliary passages and gallbladder. This excluded any expected deaths from liver cancer not specified as primary (ICD8 197.8). As mentioned above, the exposures of the different cohort members differed. Three studies used total plant employment, while Brown et al. used duration of employment in high PCB exposed areas. The observed deaths of the Brown et al. studies in Table 23 are listed both ways. However, it was not possible to similarly redistribute the expected deaths and one must recognize that some of the low duration expected deaths would move to longer durations of employment categories. We will see, however, that this inability to accurately redistribute the expected deaths has little practical effect on our consideration of the data.

The discussion of the time course of human cancer would appear to be appropriate for our consideration of the expected dose and time dependence of PCB liver and biliary tract cancer. As such, it would be expected that the ranking of relative risk, according to duration and time from onset of exposure, would correspond to that of Table 21. Rather than depict expected and observed deaths according to duration of exposure or time from onset of exposure, they are best categorized according to equally ranked risk categories. This is done in Table 24, in which the cells of Table 23 were ordered according to the relative risks of Table 21 and divided into five categories of risk. Category boundaries were set at the cell boundaries that would most closely provide equal expected risk categories. If the estimated relative risk categories reflect the actual risk categories, one would expect greater numbers of deaths to occur in those of higher relative risk. Correspondingly, with no exposure related risk, one would expect the deaths to be distributed randomly across all five categories.

As can be seen from Table 24, there is no significant trend with increasing estimated risk when the durations of exposure are periods of employment in high PCB exposed jobs. However, when the deaths in the cohort of Brown are categorized according to total plant employment, as other deaths are, the distribution corresponds to an increasing risk of cancer with increasing estimated risk. However, because of the small number of deaths, the trend does not achieve statistical significance. Note, again, that the number of deaths expected in the Brown cohort on the basis of general population statistics are not distributed by total plant employment. This would alter the location of the division lines in Table 24, most likely causing two of the cancers in the fifth or highest risk quintile (those in the 154 hypothetical risk cell) to be placed in the fourth. There would be little effect of consequence on the three lower categories.

In summary, while only seven deaths from liver and biliary tract cancer occurred, the criteria of Hill for an association with exposure are reasonably well met. The association is strong (SMR=275) and achieves statistical significance. A finding of excess cancer is present in the workforces of four of the five plants studied; the overall excess did not come from one sporadically high finding. The concordance of the animal data and the finding of liver tumors in humans exposed to dibenzofurans, structurally similar compounds, adds weight to the human evidence. The exposure and time relationship of the cancer incidence are in accord with expectations. Finally, no other exposure or circumstance could be identified that would provide an alternative explanation for the excess. Considering all the data, the evidence is strong for a causal association between the excess of these cancers and exposure to PCBs.

Cancer of the lymphatic and hematopoietic system

Tables 25 and 26 list the employment and diagnostic information for all cancers of the lymphatic and hematopoietic system found in the studies under review. Diagnosis of all of these malignancies is relatively easy and death certificate cause of death is about 85% accurate for the lymphomas and 96% accurate for the leukemias (although considerably less so for the individual cell types) (Percy et al., 1981). However, no pathological data are available for any of the cases. As mentioned previously, two lymphomas and one leukemia occurred within two years of plant hire and a third lymphoma within five years. Unless remarkable exposures occurred, these malignancies cannot be associated with PCB exposure. Elimination of consideration of the first five years from onset brings the combined lymphoma-leukemia SMR down to 130 from 138 and that from lymphomas alone from 161 to 138. Thus, the strength of an association between either or both of these two types of tumors is relatively weak and does not achieve statistical significance.

Consideration of the lymphomas and leukemias is made difficult by the fact that the category encompasses different malignancies, each with its own pathogenesis and etiology. Currently, roughly half the deaths of leukemia in the U.S. are of the myeloid type, about 30% lymphatic and the remainder largely unspecified. Of the lymphomas, about 25% are lymphosarcomas or reticulum cell sarcomas, 10% Hodgkin's disease, and 30% multiple myeloma. Ideally, we would wish to consider each disease entity separately in studying the effects of a specific chemical. This is often impossible because of the small number of deaths in a specific disease category; only extremely high relative risks could be ascertained. Thus, most studies of occupational or other exposures considered mortality in combined categories, as was done here in Tables 16-18.

Nevertheless, specific agents appear to produce malignancies of several types in this combined system. Benzene exposure leads to an increase in myeloid leukemia and multiple myeloma (Rinsky et al., 1987). Herbicide exposure has been linked to both Hodgkin's disease and non-Hodgkin's lymphoma (Hardell et al., 1980), although others did not find the association with Hodgkin's disease (Hoar et al., 1986). Radiation from atomic bomb explosions increased the risk of non-Hodgkin's lymphoma and all forms of leukemia except chronic lymphatic leukemia (Beebe et al., 1978). The NCI (1978) bioassay for PCBs showed the greatest increase in death to be from lymphatic leukemia; granulocytic leukemia was slightly increased in the two higher exposed groups and a lymphocytic and histiocytic lymphoma were found only among the highest exposed animals (see Table 6). The distribution of lymphomas in Table 25 suggests a possible increase in lymphosarcomas/reticulum cell sarcomas over the percentage in the general population, but not greatly so. The small numbers of cases preclude any analysis by subcategory in this review; the above studies suggest that subcategory analysis may not be of crucial importance.

As seen above, the overall SMR for lymphomas or for lymphomas and leukemias combined was not significant. However, the trend with expected risk is statistically significant. Let us consider the possibility of a promotional action as was done with the liver and biliary tumors; initiatory type action will be considered in the next subsection. Table 27 lists the observed deaths and those expected, based on general population data, according to years of exposure and time from onset of exposure. Tables 27a and 27b show observed and expected deaths for lymphatic cancers alone disaggregated by female and male PCB workers respectively. The ratio of observed to expected deaths by years of exposure in Table 27 indicates a significant excess for those employed 20 or more years (5 obs. vs 1.19 exp.; SMR=420; p=0.0075). Ordering the duration and time from onset cells according to the hypothetical risk categories of Table 21 as shown in Table 28 also indicates a statistically significant nonuniform distribution (X^2=12.89, p=0.013) produced by the excess of malignancies in the highest risk quintile. The finding of a significant number of tumors in

the highest risk categories is, however, weakened by the fact that half of these are leukemias, three from the cohort with the least average intensity of exposure.

All of the excess lymphoma cases occur among female PCB workers (Table 17) and three of these cases occur among women with less than five years' duration of exposure and within 5 years of first exposure (Table 27a). No dose/response gradient is evident when the data for female lymphomas are grouped according to hypothetical risk categories (Table 28a).

In considering the effect of the similar acting chemicals, the study of Hardell et al.(1981), suggesting an increase of lymphomas (and soft tissue sarcomas) from exposure to chlorophenols and phenoxy acids, has already been noted. Three cancers of the lymphatic and hematopoietic system vs. 0.88 expected were found in the follow-up of a group of workers exposed accidentally to tetrachlorodibenzodioxin (Zack and Suskind, 1980). However, neither lymphomas nor leukemias were in excess in experiments of TCDD exposed animals (Van Miller et al., 1977: Kociba et al.,1978)

In summary the evidence for an association of leukemias and lymphomas with PCB exposure is much weaker than that for the liver and biliary passages. The overall SMRs are not substantially increased. The most substantial evidence is the association of increasing risk with increasing duration of employment in PCB using industries. Animal data are supportive, but of a limited nature. Specificity of action is lacking--no single malignancy is notably increased within the system. Data from studies of similar chemicals are supportive, but the studies are limited. Overall, the evidence for an association is very suggestive, but further data are required before a definitive statement can be made on causality.

PCB effect on cancer initiation

As described in the section on the time course of cancer, PCBs may affect cancer initiation by other agents to which people are exposed by increasing or decreasing their metabolism in the liver through the stimulation of liver enzymes. The manifestation of this effect would be seen in significantly different SMRs for cancers of interest at equal times from onset of exposure among groups exposed first to PCBs at different ages. This is because the effect of additional initiation will increase the number of cancers by an amount that should be independent of the development of cancer otherwise (in contrast to promotion where the extra cancers are proportional to the number of cancers otherwise). Thus, the SMR for groups first exposed at different ages will differ because of the greatly increased number of expected cancers in groups first exposed at older ages. The contribution to the numerator of the SMR by PCB initiation action is independent of

age, while the denominator is not.

Tables 29 through 33 list the observed and expected deaths for major cancer sites among groups first exposed to PCBs at ages under 25, 25 to 34 and 35 or over. If one focuses on the SMRs of the periods of time 20 or more years from first exposure (when initiation-related cancers are most likely to occur), there is no evidence in any of the sites analyzed for a PCB-related initiation effect, either increasing or decreasing the risk of cancer overall or of the lung, breast or colon and rectum. The SMRs for all cancer for the three age groups, <25, 25-34 and 35+ are, respectively, 86, 77 and 80. These SMRs are not significantly different. Further, if we delete the cancers of the liver and biliary tract and the lymphatic and hematopoietic system from this consideration (because they are likely to be due to a promotional action if they are PCB related), the respective SMRs become 75, 78 and 75.

A secondary, but noteworthy, outcome of this analysis is that the cancer risks 20 or more years from onset of exposure of the cohorts reviewed here are significantly less than that expected from general population statistics. The above analysis provides no evidence that this is a PCB related effect. Selection factors relating to life style or residence may account for these deficits. Thus, any epidemiological bias that may be present in this analysis from the use of general population rates is likely to lead to an underestimation of an effect. This adds strength to the findings for cancer of the liver, biliary tract and gallbladder and for the lymphatic and hematopoietic system.

3.7 SUMMARY

A review or "meta-analysis" has been conducted of all the available data relating to the cancer mortality risk of workers exposed to PCBs during the manufacturing of electrical capacitors. This analysis was performed with the cooperation of all researchers who undertook the initial studies, each of whom provided data and analyses for this review. This cooperation was of particular importance as it allowed data from different studies and different nations to be combined according to time and exposure variables of importance for identifying a potential PCB effect. These time and exposure variables of importance were identified from models of the age, time and exposure dependence of cancer from exogenous agents and from experimental data on cancer risk.

The results of the analysis provide strong evidence that PCBs produce cancer of the liver, biliary tract and gallbladder in humans. While only seven such deaths were identified in all studies, the high and statistically significant SMR, 275, is strengthened by the concordance of animal data, results of human exposure to chemically similar compounds and the observation of an

appropriate time and exposure relationship with cancer risks. The review also suggests an increased risk of cancer of the lymphatic and hematopoietic system. Here, however, the overall evidence is less strong and further data are required before a definitive statement can be made on causality. Cancers of the rectum, kidney and urinary bladder were also elevated in the combined analysis. However, the numbers of malignancies at these sites were too few to allow any statement to be made on a relationship with PCB exposure.

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TABLE 1

EQUITOXIC LEVELS OF POLYHALOGENATED POLYAROMATIC COMPOUNDS IN THE FOOD OF RHESUS MACAQUES

Compound	Polyhalogenated polyaromatic (ng/g food)
Aroclor 1242	100,000
Aroclor 1248	25,000
Firemaster FF-1	25,000
3,4,3',4'-Tetrachlorobiphenyl	1,000
3,4,5,3',4',5'-Hexachlorobiphenyl	1,000
2,3,7,8-Tetrachlorodibenzofuran	50
2,3,4,6,7,8-Hexachlorodibenzo-p-dioxin	5
2,3,6,7-Tetrachlorodibenzo-p-dioxin	0.5-2

From: McNulty (1985)

TABLE 2

THE COMPOSITION AND DEGREE OF CHLORINATION OF COMMERCIAL MIXTURES OF PCBs

Commercial PCB Product	Percent Chlorine	Percentage of isomers with indicated number of chlorine atoms										Estimated Dibenzofuran Contamination (ppm)
		1	2	3	4	5	6	7	8	9	10	
Kanechlor 500	54[a]			5	26	55	13					4[b]
Kanechlor 400	47[a]		3	33	44	16	5					18[b]
Kanechlor 300												1[b]
Aroclor 1260	60											3.8[c]
Aroclor 1254	54[d]			1	21	48	23	6				0.2-1.9[c]
Aroclor 1242	42[e]	1	17	52	25	5						0.2
Aroclor 1016	41[e]	2	19	56	21	1						<0.005
Pyraline 3010	42[d]		9	60	30	1						2.0[c]

a. Kimbrough et al. (1975)
b. Kuratsune et al. (1976)
c. Busar (1985)
d. Mieure et al. (1976)
e. Albro and Parker (1976)

TABLE 3

HISTOPATHOLOGICAL FINDINGS IN THE LIVER OF MALE WISTAR RATS GIVEN POLYCHLORINATED BIPHENYLS (PCBs)

PCB in diet (ppm)		Cholangiofibrosis (%)	Nodular Hyperplasia (%)
Kanechlor-500	(1000)	4/13	5/13
	(500)	0/16	5/16
	(100)	0/25	3/25
Kanechlor-400	(1000)	2/10	3/10
	(500)	0/8	0/8
	(100)	0/16	2/16
Kanechlor-300	(1000)	2/15	0/15
	(500)	0/22	1/22
	(100)	0/18	0/18

From: Ito et al. (1974)

TABLE 4

INCIDENCE AND TYPE OF LIVER LESIONS AND TUMORS
OF OTHER ORGANS AMONG FEMALE SHERMAN RATS
EXAMINED HISTOLOGICALLY

Organ or Tissue	Type of Lesion	Incidence	
		Controls	Experimental
Liver	Hepatocellular carcinoma	1/173	26/184
	Neoplastic nodules	0/173	144/184
	Foci or areas of cytoplasmic alteration	28/173	182/184
Thyroid gland	Parafollicular cell tumor	37/160	18/166
Adrenal gland	Pheochromocytoma	1/173	1/167
Pituitary gland	Chromophobe adenoma	41/153	28/139
	Carcinoma	0/153	1/139
Uterus	Endometrial polyp	18/149	25/163
	Adenocarcinoma	0/149	2/163
	Sarcoma of endometrial stroma	3/149	7/163
Urinary Bladder	Transitional cell papilloma	1/167	0/169
Mammary gland	Fibroadenoma	17/173[a]	13/184[a]
	Adenocarcinoma	5/173[a]	1/184[a]
Salivary gland	Fibrosarcoma	1/173[a]	0/184[a]
Lung	Adenoma	2/173	2/184
Adipose tissue	Lipoma	0/173[a]	2/184[a]
Brain	Glioma	0/173	2/184
Ovary	Granulosa theca cell tumor	5/149	0/163
	Papillary adenoma	1/149	2/163
Hematopoietic system	Granulocytic leukemia	1/17	0/184
	Lymphoma	0/173	2/184
Kidney	Hemangioma	0/173	1/184
Thymus	Thymoma	0/173[a]	0/184[a]
Parathyroid gland	Adenoma	0/173	2/184
Skin	Fibroma	0/173[a]	1/184[a]

Exposure: 100 ppm Aroclor 1260 in diet from 3 weeks to 22 months.
[a]Incidence based on gross detection with microscopic confirmation.
From: Kimbrough et al. (1975).

TABLE 5

INCIDENCE OF LIVER LESIONS IN ALBINO RATS TREATED WITH AROCLORS FOR TWO YEARS

	Control	Aroclor 1242			Aroclor 1254			Aroclor 1260		
Diet level, ppm	0	1	10	100	1	10	100	1	10	100
No. of animals examined	23	32	29	16	30	26	26	26	25	25
Focal hypertrophy hepatocytes	0	2	3	8	3	4	14	3	13	9
Nodular hyperplasia	1	1	1	8	0	3	14	0	7	6
Ductal hyperplasia	5	3	3	3	6	3	14	6	7	12
Hepatoma	0	0	0	3	0	0	4	0	1	7
Cholangiohepatoma	0	0	0	1	0	0	2	0	0	4
Hepatocellular carcinoma	0	0	0	0	0	0	0	0	0	0

From: Levinskas (1981); preliminary data were given by Calandra (1975).

TABLE 6

INCIDENCE OF LIVER LESIONS AND CARCINOMAS IN SELECTED TISSUES AMONG FISHER 344 RATS FED AROCLOR 1254

		Number of animals with tumors* Aroclor 1254 conc. (ppm)							
		Controls		25		50		100	
Organ or tissue	Type of lesion	M	F	M	F	M	F	M	F
Lung/bronchus	Carcinoma	1	0	0	0	0	0	0	0
	Adenoma	0	1	0	0	2	1	2	0
	Papilloma	0	0	1	0	0	0	0	0
	Hamartoma	0	0	1	0	0	0	0	0
Stomach	Adenocarcinoma	0	0	0	1	1	1	0	0
	Adenoma	0	0	0	0	0	0	0	1
Jejunum	Carcinoma	0	0	0	0	0	0	1	0
Cecum	Adenocarcinoma	0	0	0	0	1	0	0	0
Liver	Hepatocellular Carcinoma	0	0	0	0	1	0	2	0
	Undifferentiated Carcinoma	0	0	0	1	0	0	0	0
	Adenoma	0	0	0	0	0	0	1	2
Pituitary	Adenoma	0	4	2	1	0	1	0	1
Adrenal	Adenoma	1	0	0	0	0	0	0	0
Leukaemia	Lymphocytic	0	1	0	2	0	1	4	0
	Granulocytic	3	3	2	4	5	5	4	4
Lymphoma	Lymphocytic	0	0	0	0	0	0	0	1
	Histiocytic	0	0	0	0	0	0	0	1
	N O S	0	0	0	0	0	0	1	0
Testis	Interstitial cell tumor	24		24		20		20	
Scrotum	Fibroma	1		0		0		0	
Mammary gland	Adenocarcinoma		0		4		0		0
	Adenoma		1		0		0		0
Uterus	Adenocarcinoma		0		1		0		1
	Adenoma		0		0		0		1
	Leiomyoma		0		1		0		0
Ovary	Granulosa-cell tumor		0		1		0		0
Other		3	0	2	4	2	2	2	2
Total with malignant tumors		5	4	2	13	9	8	12	9
Total with benign tumors		24	7	24	8	20	8	21	7

*Twenty-four animals in each group
From: NCI (1978)

TABLE 7

INCIDENCE OF LIVER LESIONS AND CARCINOMAS AMONG SPRAGUE-DAWLEY RATS FED AROCLOR 1260

	CONTROLS		EXPOSED	
	MALE	FEMALE	MALE	FEMALE
No. of animals examined	32	49	46	47
Adenocarcinomas	0	0	0	24
Trabecular carcinomas[a]	0	0	2	19
Neoplastic nodules[b]	0	1	5	2
Cholangioma (simple)	2	2	14	21
Cholangioma (cystic)	0	1	2	5
Adenofibrosis	2	1	1	7

a. Animals with trabecular carcinomas and adenocarcinomas were placed only in the adenocarcinoma category.

b. Animals with neoplastic nodules and carcinomas were placed only in the relevant carcinoma category.

Exposure: 100 ppm in diet for 16 months following weaning, then 50 ppm for an additional 8 months.

From: Norback and Weltman (1985).

TABLE 8

INCIDENCE OF LIVER LESIONS AMONG MALE dd MICE FED BENZENE HEXACHLORIDE AND KANECHLOR 500

EXPOSURE CONDITIONS	INITIATING CHEMICAL	CONC. (PPM)	PCB	PCB CONC. (PPM)	NO. OF ANIMALS	NO. WITH NODULAR HYPERPLASIA	NO. WITH HEPATOCELLULAR CARCINOMA
24 weeks (from a weaning in diet) Male dd Mice	- BHC	250	Kanechlor 500	0	30	23	8
				250	26	21	15
		100		0	26	0	0
				250	25	8	1
		50		0	28	0	0
				250	30	9	2
	- BHC	250	Kanechlor 500	0	26	0	0
				250	29	16	6
		100		0	26	0	0
				250	30	5	1
		50		0	28	0	0
				250	29	0	0
	- BHC	250	Kanechlor 500	0	26	0	0
				250	28	0	0
		100		0	28	0	0
				250	30	0	0
		50		0	28	0	0
				250	27	0	0
	NONE			250	20	0	0
	CONTROLS				20	0	0

BHC = benzene hexachloride

From: Ito et al. (1973)

TABLE 9

INCIDENCE OF LIVER TUMORS PRODUCED IN RATS TREATED WITH Ph-Na, DDT, AND/OR PCB AFTER DENA EXPOSURE[a]

Group No.	Treatment	Average number of liver tumors (> 5 mm), per rat 40 wk.		52 wk.	
1	DENA	0	(0, 0, 8)	0	(0, 0, 8)
2	DENA+Ph-Na	0.6 0.3	(4, 3, 7)	1.0 0.5[b]	(8, 4, 8)
3	DENA+DDT	0.2 0.2	(1, 1, 6)	0.4 0.2	(3, 3, 8)
4	DENA+PCB	3.3 0.7[C]	(23, 6, 7)	6.9 2.1[C]	(55, 8, 8)
5	DENA+Ph-Na, DDT	0.4 0.3	(3, 2, 8)	0.5 0.3	(4, 3, 8)
6	DENA+Ph-Na, PCB	3.4 1.5[b]	(24, 4, 7)	3.6 1.3[b]	(32, 7, 9)
7	DENA+DDT, PCB	1.0 0.5[d]	(9, 4, 9)	4.4 1.6[c]	(31, 7, 7)
8	DENA+Ph-Na, DDT, PCB	0.1 0.1[e]	(1, 1, 8)	2.6 1.3[b]	(18, 6, 7)
9	Olive Oil	0	(0, 0,10)	0	(0, 0, 8)
10	No treatment	0	(0, 0, 9)	0	(0, 0, 9)

[a]Abbreviations: Ph-Na, phenobarbitol sodium; DEN, diethylnitrosamine.
[b]Significantly different from the value in group 1 ($P<0.05$).
[c]Significantly different from the value in group 1 ($P<0.01$).
[d]Significantly different from the value in group 4 ($P<0.05$).
[e]Significantly different from the value in group 4 ($P<0.01$).

Exposure: DENA, 50 ppm for 2 wks; Ph-Na, 500 ppm in drinking water for 12 wks;
DDT, 0.1 ml of 1.25% soln. 2x/wk by intubation for 12 wks;
PCB, 0.1 ml. of 10% sol'n. 2x/wk. by intubation for 12 wks.

From: Nishizumi, M., (1979).

TABLE 10

HISTOPATHOLOGIC LIVER LESIONS IN MALE RATS TREATED WITH PCB AND VARIOUS CHEMICAL CARCINOGENS: PRESTON ET AL. DATA

Group (treatment)	No. of rats	Hepatocyte lesions		
		Foci of cellular alteration[a]	Neoplastic nodules[b]	Hepato-cellular carcinoma
I (control)	72	0	0	0
II (DENA)	32	10	6	5
III (AR 1254)	34	0	0	0
IV (DENA and AR 1254)	33	0[c]	10	21[c]
V (AR 1254 + CDF)	34	0	0	0
VI (DENA and AR 1254 + CDF)	32	1[c,d]	5[d]	27[c,d]

a. Animals had foci of cellular alteration but no neoplastic nodules or hepato-cellular carcinomas.
b. Animals had neoplastic nodules but no hepatocellular carcinomas.
c. Significantly different from group II ($P<0.05$).
d. Not significantly different from group IV($P>0.05$).

From: Preston et al. (1981)

TABLE 11

HISTOPATHOLOGIC LIVER LESIONS IN MALE RATS

TREATED WITH PCB AND VARIOUS CHEMICAL CARCINOGENS:
MAKIURA ET. AL. DATA

	Group[a]	Experimental period (wk)[b]	Initial No.of rats	Effective No. of rats[c]	No. with Nodular Hyper-plasia	No with Hepato-cellular carcinom
1.	3'-Me-DAB	24.0	23	23	22	15
2.	2-FAA	24.0	16	13	13	7
3.	DEN	23.6	16	13	13	12
4.	PCB	24.0	24	19	0	0
5.	PCB+3'-Me-DAB	24.0	24	23	0	0
6.	PCB+2-FAA	24.0	24	17	1	0
7.	PCB+DEN	23.3	16	9	0	0
8.	3'-Me-DAB+DEN	23.8	16	13	13	12
9.	2-FAA+DEN	20.5	16	11	11	9
10.	PCB+3'-Me-DAB+DEN	24.0	16	13	4	1
11.	PCB+2-FAA+DEN	23.7	16	12	3	0
12.	Control	24.0	12	10	0	0

[a]Concentration in diet: PCB, 500 ppm Kanechlor 500; 3'-Me-DAB, 300 ppm; 2-FAA, 150 ppm; DEN, 25 ppm

[b]Animals fed experimental diet for 20 wk and then stock diet for 4 wk. Numbers <24 indicate that rats died before 24 wk.

[c]Rats that died within 16 wk from start of experiment were excluded from initial number.

From: Makiura et al. (1974)

TABLE 12

EFFECT OF PCB EXPOSURE ON BLOOD ENZYME CONCENTRATIONS

Study	No. of subjects	Average PCB conc. (ppb serum)	Correlation with serum PCB SGOT	SGPT	GGTP	Alk P	LDH	Bili
Baker et al. (1980)	148	17-75[a]	NS	NS	NS	NS	NS	NS
Maroni et al. (1981b)	80	41-1319[b]	NS	(+)	(+)			
Kreiss et al. (1981)	458	3-158[b]		NS	+			NS
Chase et al. (1982)	120	10-312	+	NS	NS			
Smith et al. (1982)	317	1-3300L[bc]	+	NS	+	NS	NS	NS
		1-250H[bc]	+	NS	+	NS	NS	NS
Fischbein (1985)	227	48L- 124H[d]	NS	NS	+male	NS	+fem	NS
Lawton et al. (1985)	194	57-2270L[e]	NS	NS	+	NS	NS	-
		12-392H[e]	NS	NS	+	NS	NS	-
Emmett (1985)	55	1-300[b]	NS	NS	+	NS	NS	NS
Nethercott and Holness (1986)	176	<20, >20[f]	NS			NS		NS

NS=Not significant
+ = Significant positive correlation
- = Significant negative correlation
a. Range of group means
b. Range of individual means
c. L = low chlorinated PCBs, H = high chlorinated PCBs
d. Study population means
e. 95 % range
f. Serum concentration categories

TABLE 13

EFFECT OF PCB EXPOSURE ON BLOOD LIPID CONCENTRATIONS

Study	No. of subjects	Average PCB conc. (ppb serum)	Correlation with serum PCB Cholesterol	Triglycerides
Baker et al. (1980)	148	17-75[a]	NS	+
Kreiss et al. (1981)	458	3-158[b]	+	NS
Chase et al. (1982)	120	10-312	NS	+
Smith et al. (1982)	317	1-3300L[bc]	+	NS
		1-250H[bc]	+	+
Fischbein et al. (1979)	321	48L- 124H[d]	(+)	NS
Lawton et al. (1985)	194	57-2270L[e]	NS	NS
		12-392H[e]	NS	NS
Emmett (1985)	55	1-300[b]	NS	NS
Nethercott and Holness (1986)	176	<20, >20[f]	NS	+

NS=Not significant
+ = Significant positive correlation
- = Significant negative correlation
a. Range of group means
b. Range of individual means
c. L = low chlorinated PCBs, H = high chlorinated PCBs
d. Study population means
e. 95 % range
f. Serum concentration categories

TABLE 14

EXPOSURE MEASUREMENTS IN PLANTS FROM WHICH PCB EXPOSED COHORTS WERE ESTABLISHED

Activity	NY (Brown 1, Nicholson) NIOSH (1977)[a]	Company 1975)[b]	MA (Brown 2) NIOSH (1977)[a]
	United States Plants		
	(ug/m^3)		
Degrease			855 (4)
Treat, impregnation, seal	175 (8)	792 (4)	791 (20)
Quality control, test, salvage	207 (16)	410 (1)	309 (8)
Assembly	99 (6)	251 (3)	
Case fabrication, foil production, winding, pre-assembly	43 (7)	40 (2)	92 (13)
Packing, shipping	109 (8)		90 (2)
Maintenance	150 (1)		280 (1)
	Italian Plant (Bertazzi)		
	Maroni (1977)[c]		
High power capacitors	154 (4)		
Low power capacitors	193 (3)		
Small household capacitors	59 (2)		
	Swedish Plant		
	(1973)[d]		
Unspecified exposure	100 (?)		

a. NIOSH industrial hygiene surveys of March and April, 1977, quoted in Brown et al. (1981). Use of PCBs had recently been reduced to 25% of former usage.
b. Company industrial hygiene information (Personal communication)
c. Maroni et al. (1981a)
d. Gustavsson et al. (1986)

TABLE 15

CHARACTERISTICS OF FOUR PCB MORTALITY STUDIES

Characteristic	Brown (1986)	Gustavsson et al. (1986)	Bertazzi et al. (1987)	Nicholson et al. (1987)
No. of subjects				
Male	1258	142	594	447
Female	1309	0	1556	322
Minumum period of employment	3 mo.	6 mo.	1 wk.	5 yr.
First year of follow-up	1940	1965	1946	1956
Final year of follow-up	1982	1980	1982	1982
Minimum latency	3 mo.	6 mo.	1 wk.	10 yr.
Number of deaths				
Male	141	21	30	137
Female	154	NA	34	51
Tracing Completeness	96.2%	100.0%	99.5%	98.6%
Average employment duration	3.4 y[a]	6.5 y[b]	<5 y[c]	17.7 y[c]
Calendar years of plant PCB usage	38/46/51-77[d]	60-78	46-80	46/51-77[d]

a. Employment duration is that in "PCB exposed" jobs.
b. Cohort members were those employed in work having direct PCB exposure.
c. Cohort members included all plant employees.
d. Three separate complexes of the companies were included in the cohort of Brown. Two of the same plant complexes of one company were studied by Nicholson et al. The onset of PCB use is as indicated in the three facilities.

TABLE 16

EXPECTED AND OBSERVED CANCER MORTALITY AMONG PCB EXPOSED MALE CAPACITOR MANUFACTURING WORKERS IN FIVE COHORTS

	ICD8	Bertazzi		Brown 1		Brown 2		Gustavsson		Nicholson		TOTAL	
use of Death		E	O	E	O	E	O	E	O	E	O	E	O
ll causes	00-999	30.88	30	88.28	80	71.69	61	22.12	21	45.49	43	258.46	235
rdiovascular disease	390-458	7.73	8	36.89	43	26.57	30	11.40	8	58.09	53	140.68	142
ll malignant neoplasms	140-209	7.24	14	17.66	10	13.65	7	5.39	7	23.98	19	67.92	57
harynx, buccal cavity	146-149	0.25[a]	0	0.43	0	0.33	0	0.08[a]	0	0.67[a]	1	1.76	1
sophagus	150	0.19[b]	0	0.41	0	0.30	0	0.12[b]	0	0.62[a]	1	1.64	1
tomach	151	1.08[b]	2	0.80	0	0.56	1	0.66[b]	0	1.06[a]	0	4.16	3
ntestine, except rectum	153	0.35[c]	0	1.55	1	1.15	0	0.41[c]	0	2.67	2	6.13	3
ectum	154	0.21[c]	0	0.49	1	0.35	0	0.22[c]	0	0.82	1	2.09	2
iver, biliary passages and gall bladder	155-156	0.22	2	0.27	1	0.20	0	0.23	1	0.32	0	1.24	4
ancreas	157	0.24[b]	2	0.94	0	0.70	1	0.36[b]	0	1.29[a]	1	3.53	4
arynx	161	0.27[a]	0	0.26	0	0.19	0	0.03[a]	0	0.32[a]	0	1.07	0
ronchus, trachea, lung nd other respiratory	162-163	1.75	3	6.05	5	4.63	0	1.05	2	7.97	6	21.45	16
one	170	0.09[a]	0	0.09	0	0.10	0	0.03[a]	0	0.11[a]	0	0.42	0
kin	172-173	0.06[a]	0	0.40	0	0.36	1	0.08[a]	0	0.37[a]	0	1.27	1
rostate	185	0.47[a]	1	0.92	0	0.56	1	0.90[a]	1	2.30[a]	2	5.15	5
rinary bladder	188	0.30[a]	0	0.45	1	0.31	1	0.18[a]	1	0.88[a]	0	2.12	3
idney	189	0.10[a]	0	0.46	1	0.35	1	0.14[a]	1	0.54[a]	1	1.59	4
rain, nervous system	191-192	0.12[a]	1	0.66	0	0.59	0	0.19[a]	0	0.58[a]	0	2.14	1
ymphomas	200-203	0.46	1	1.08	0	0.95	1	0.31	1	1.21	1	4.01	4
eukemias	204-207	0.41	2	0.74	0	0.65	0	0.22	0	0.85	2	2.87	4
ll other malignancies		0.67	0	1.66	0	1.37	0	0.18	0	1.40	1	5.28	1

E=Expected
O=Observed

a. Estimated from the ratio of national age standardized site rates to all cancer rates (1975) times the study expected deaths for all cancer.
b. Estimated from the ratio of national age standardized site rates to all GI cancer rates (1975) times the study expected deaths for all GI cancer.
c. Estimated from the ratio of national age standardized site rates to combined colon-rectum cancer rates (1975) times the study expected deaths for all cancer.

TABLE 17

EXPECTED AND OBSERVED CANCER MORTALITY AMONG PCB EXPOSED FEMALE CAPACITOR MANUFACTURING WORKERS IN FIVE COHORTS

	ICD8	Bertazzi		Brown 1		Brown 2		Nicholson		TOTA
Cause of Death		E	O	E	O	E	O	E	O	E
All causes	00-999	25.03	34	41.96	36	115.55	118	45.49	43	228.03
Cardiovascular disease	390-458	4.29	2	13.53	15	38.56	32	20.04	11	76.42
All malignant neoplasms	140-209	8.80	12	13.49	8	34.84	37	14.35	18	71.48
Pharynx, buccal cavity	146-149	0.08[a]	1	0.15	1	0.36	1	0.20[a]	0	0.79
Esophagus	150	0.06[b]	0	0.11	0	0.27	0	0.15[a]	0	0.59
Stomach	151	0.81[b]	1	0.37	0	1.01	0	0.51[a]	1	2.70
Intestine, except rectum	153	0.49[c]	0	1.38	2	3.67	5	1.77	0	7.31
Rectum	154	0.20[c]	0	0.30	0	0.81	3	0.38	1	1.69
Liver, biliary passages and gall bladder	155-156	0.18	0	0.24	0	0.65	3	0.23	0	1.30
Pancreas	157	0.19[b]	0	0.56	1	1.47	0	0.73	0	2.95
Larynx	161	0.03[a]	0	0.04	0	0.10	1	0.05[a]	0	0.22
Bronchus, trachea, lung and other respiratory	162-163	0.36	1	1.65	2	4.01	2	1.91	4	7.93
Bone	170	0.09[a]	0	0.05	0	0.14	0	0.07[a]	0	0.35
Skin	172-173	0.08[a]	0	0.20	0	0.53	0	0.19[a]	1	1.00
Breast	174	1.99	2	3.28	1	8.28	8	3.76	5	17.32
Uterine cervix	180	0.08[a]	0	0.67	1	1.78	2	0.47[a]	0	3.00
Other uterus	181-182	0.77[a]	0	0.46	0	1.25	1	0.47[a]	1	2.95
Ovary, fallopian tube	183	0.33[a]	1	1.07	0	2.73	3	0.97[a]	1	5.10
Urinary bladder	188	0.11[a]	0	0.13	0	0.37	0	0.22[a]	1	0.83
Kidney	189	0.10[a]	0	0.20	0	0.51	0	0.24[a]	0	1.05
Brain, nervous system	191-192	0.16[a]	1	0.47	0	1.01	0	0.39[a]	0	2.03
Lymphomas	200-203	0.90	4	0.66	0	1.75	4	0.73	1	4.04
Leukemias	204-207	0.84	0	0.41	0	1.14	0	0.43	2	2.82
All other malignancies		0.95	1	1.09	0	3.00	4[d]	0.48	0	5.52

E=Expected; O=Observed

a. Estimated from the ratio of national age standardized rates to all cancer rates (1975) ti the study expected deaths for all cancer.

b. Estimated from the ratio of national age standardized rates to all GI cancer rates (1975) times the study expected deaths for all GI cancer.

c. Estimated from the ratio of national age standardized rates to combined colon-rectum cance rates (1975) times the study expected deaths for combined colon-rectum cancer.

d. Includes one malignancy certified as liver cancer (NOS), ICD8, 197.8. Pathology analysis showed the tumor to be metastatic from another site.

TABLE 18

SUMMARY OF OBSERVED AND EXPECTED CANCER DEATHS AMONG FIVE COHORTS OF PCB CAPACITOR MANUFACTURING WORKERS

	Obs.	Exp.	SMR	
All malignancies	132	139.40	95	
Pharynx, buccal cavity	4	2.55	157	
Esophagus	1	2.23	45	
Stomach	5	6.86	73	
Intestine, except rectum	10	13.44	74	
Rectum	6	3.78	159	p=0.17[a]
Liver, biliary passages and gallbladder	7	2.54	275	p=0.015
Pancreas	5	6.48	77	
Larynx	1	1.29	78	
Bronchus, trachea, lung and other respiratory	25	29.38	85	
Bone	0	0.77	0	
Skin	2	2.27	88	
Female breast	16	17.32	92	
Female genital organs	10	11.05	90	
Prostate	5	5.15	97	
Urinary bladder	4	2.95	136	)
Kidney	4	2.64	152	) p=0.20
Brain, nervous system	2	4.17	48	
Lymphomas	13	8.05	161	p=0.066
Leukemias	6	5.69	105	
All other malignancies	6	10.80	56[b]	

a. p values are one-sided, values of 0.20 or less are indicated.
b. Includes one cancer certified as liver cancer (NOS): ICD8, 197.8; pathology specimen showed cancer to be metastatic from another site.

TABLE 19

EXPECTED[a] AND OBSERVED DEATHS AMONG PATIENTS WITH YUSHO

Cause of death	Observed and expected deaths					
	Male			Female		
	O	E	SMR	O	E	SMR
All causes	79	66.1	119	41	48.9	84
All malignant neoplasms	33	15.5	213	9	10.6	76
Stomach	8	5.7	140	0	3.3	0
Liver	9	1.6	559	2	0.7	304
	9	2.3[b]	385	2	0.8[b]	253
Lung, trachea, bronchus	8	2.5	326	0	0.9	0
Heart diseases	10	9.5	106	9	7.7	118
Cerbrovascular disease	8	14.6	55	5	12.0	42
Liver disease	6	2.3	265	2	0.7	274

a. Expected deaths calculated using national rates.
b. Expected deaths calculated using rates of Fukuoka and Nagasaki prefectures.

From: Kuratsune et al. (1986)

TABLE 20

PEAK PCB CONCENTRATIONS AND ESTIMATED ISOMER HALF-LIVES FROM CONCENTRATIONS MEASURED IN INDIVIDUALS 45 MONTHS APART

PCB Peak	No. of Subjects	Concentrations (ug/l) 1976	1979	Ratio	$T_{1/2}$ (Years)
2',4,4' tri-	165	24.1	14.0	0.58	5
2,2',4,4' tetra 2,2',4,5' tetra- 2,2',5,5' tetra-	145	3.9	2.8	0.71	8
2,3',5,5' tetra-	76	2.3	0.4	0.17	2
2.,4,4',5 tetra- 2,3',4,4' tetra-	165	13.8	15.4	1.12	-
2,2',4,4',5 penta- 2,2',4,5,5' penta-	155	3.6	2.7	0.74	9
2,3',4,4',5 penta-	155	3.1	2.7	0.89	24
2,3,3',4,4', penta- 2,2',4,4',5,5' hexa-	159	2.3	3.8	1.62	-
2,2',3,4,4',5' hexa-	159	3.2	2.9	0.91	29

From: Wolff (1987)

TABLE 21

HYPOTHETICAL RELATIVE RISK FOR PCB PROMOTIONAL CANCER ACTION ACCORDING TO DURATION OF EXPOSURE AND TIME FROM ONSET OF FIRST EXPOSURE

Years of Exposure	Time from onset of exposure (years)							
	<5	5-9	10-14	15-19	20-24	25-29	30-34	35-39
<5	1.00	1.11	1.11	1.08	1.06	1.04	1.03	1.02
5-9		1.16	1.36	1.29	1.20	1.14	1.10	1.07
10-14			1.45	1.54	1.41	1.29	1.20	1.14
15-19				1.58	1.67	1.50	1.35	1.25
20-24					1.70	1.76	1.56	1.40
25-29						1.79	1.82	1.60
30-34							1.85	1.87

TABLE 22

CASES OF LIVER, BILIARY TRACT AND GALLBLADDER CANCER IN FIVE COHORTS OF PCB EXPOSED WORKERS

Study	Sex	Date first exposed	Age at hire	Duration of exposure	Date of death	Death certificate cause of death	Pathology confirmation
Bertazzi	M	1957	33	0.3y	1974	Primary liver cancer (ICD8 155)	Not yet confirmed
Bertazzi	M	1959	41	1.0y	1973	Biliary tract cancer (ICD8 156)	Not yet confirmed
Brown 1	M	1949	25-35	1\10y[a]	1958	Primary carcinoma of liver with metastasis (ICD7 155.0)	Confirmed as intrahepatic bile duct cancer
Brown 2	F	1954	>35	1.5\14.3y	1962	Carcinoma of the biliary system (ICD7 155.1)	No reports available
Brown 2	F	1949		9.8\28y	1979	Carcinoma of the gall bladder (ICD8 156.0)	Adenocarcinoma of liver and gall bladder. Origin probably gall bladder, metastatic to liver.
Brown 2	F	1956		0.8\3.5y	1979	Bile duct cancer (ICD8 156.1)	Cancer of the bile ducts. Origin probably from bile ducts. A history of cancer of the uterus.
Brown 2	F	1955		0.3\0.3y	1970	Carcinoma of the liver (ICD8 197.8)	Hepatic coma due to hepatoma, due to metastatic disease, primary site unknown.
Ostavsson	M	1960	27	11y	1978	Cancer of the ampulla of Vater (ICD8 156.2)	Confirmed

a. The first period is the duration of employment in "PCB exposed" jobs; the second period is the duration of plant employment.

TABLE 23

EXPECTED AND OBSERVED DEATHS FOR CANCER OF THE LIVER, BILIARY TRACT AND GALLBLADDER AMONG PCB WORKERS

Years of Exposure	Time from onset of exposure 0-4	5-9	10-14	15-19	20-24	25- 29	30+	TOTAL
				EXPECTED DEATHS				
<5	.163	.169	.191	.192	.198	.166	.116	1.195
5-9		.093	.079	.085	.083	.078	.054	.469
10-14			.114	.073	.066	.058	.054	.365
15-19				.099	.065	.055	.048	.269
20-24					.061	.050	.036	.146
25+						.036	.054	.091
TOTALS	.163	.262	.384	.449	.473	.443	.362	2.535
				OBSERVED DEATHS[a]				
<5		2*	1(1)	1(1)	1*	(1)		5(3)
5-9			(1)			1*		1(1)
10-14				1(2)				1(2)
15-19								
20-24								
25+						(1)		(1)
TOTALS		2	1(2)	2(3)	1	1(2)		7(7)

a. Open numbers utilize durations of exposure in high PCB exposed work areas for the Brown cohorts only. The four cases so affected are indicated by *. Numbers in parentheses are distributed according to total plant employment. Note, however, that the corresponding adjustments to total plant employment for the Brown cohorts was not possible for expected deaths.

TABLE 24

DEVELOPMENT OF ESTIMATED RELATIVE RISK CATEGORIES
FOR CANCER OF THE LIVER, BILIARY TRACT AND GALLBLADDER

Hypothetical relative risk	Number of deaths in cell		Number of deaths in relative risk category	
	Expected	Observed	Expected	Observed
100	.163			
103	.116			
104	.166	(1)	..445	(1)
106	.198	1		
108	.193	1 (1)		
110	.054		.445	2 (1)
111	.169,.191	2,1 (1)		
114	.078	1		
116	.093		.531	4 (1)
120	.054,.083			
129	.058,.085			
135	.048			
136	.079	(1)		
141	.066			
145	.114		.587	(1)
150	.055			
154	.073	1 (2)		
156	.036			
158	.099			
167	.065			
170	.061			
176	.050			
179	.036	(1)	.529	1 (3)
182	.054			

( ) Indicates number of cases using total plant employment as a surrogate for duration of exposure for the liver cancers of Brown.

TABLE 25

CASES OF LYMPHOMAS IN FIVE COHORTS OF PCB EXPOSED WORKERS

Study	Sex	Date employed	Age at hire	Duration of exposure	Date of death	Cause of death	ICD8 Rubri
Bertazzi	M	1952	27	7.0 y	1967	Reticulum cell sarcoma	200
Bertazzi	F	1960	20	21.8 y	1982	Hodgkins disease	201
Bertazzi	F	1949	19	12.2 y	1962	Hodgkins disease	201
Bertazzi	F	1960	17	.2 y	1961	Hodgkins disease	201
Bertazzi	F	1968	24	.7 y	1969	Lymphosarcoma	200
Brown 2	F	NA	<25	5-10y[a]	NA	Lymphosarcoma\ Reticularsarcoma	200
Brown 2	F	NA	35+	b	NA	Lymphosarcoma\ Reticularsarcoma	200
Brown 2	F	NA	35+	b	NA	Lymphosarcoma\ Reticularsarcoma	200
Brown 2	F	NA	35+	b	NA	Other neoplasms of Lymphatic and Hema-topoietic Tissue	202-203
Brown 2	M	NA	25-35	20-25y	NA	Other neoplasms of Lymphatic and Hema-topoietic Tissue	202-203
Nicholson	F	1950	33 y	7 y	1976	Lymphosarcoma of Right Lung	200.1
Nicholson	M	1952	24 y	24 y	1982	Multiple myeloma	203
Gustavsson	M	1964	59	.5 y	1975	Other neoplasms of lymphatic and hema-topoietic tissue	202

a. Only categorical data available
b. The three durations of exposure are <5 years, between 5 to 10 years, and between 20 to 25 years; a particular duration cannot be associated with a specific individual.

TABLE 26

CASES OF LEUKEMIAS IN FIVE COHORTS OF PCB EXPOSED WORKERS

Study	Sex	Date Employed	Age at hire	Duration of exposure	Date of death	Cause of death	ICD8 Rubri
Bertazzi	M	1961	21	19 y	1980	Acute myeloctic leukemia	205
Bertazzi	M	1967	32	2.2 y	1969	Acute hemocytoblastic leukemia	205
Nicholson	F	1947	39	23 y	1978	Acute myeloctic leukemia	205
Nicholson	F	1951	38	16 y	1967	Acute atom cell leukemia	207
Nicholson	M	1946	40	11 y	1959	Chronic lymphocyte leukemia	204
Nicholson	M	1946	37	21 y	1968	Acute lymphocyte leukemia	204

TABLE 27

EXPECTED AND OBSERVED DEATHS FOR CANCER OF THE LYMPHATIC AND HEMATOPOIETIC SYSTEM AMONG PCB WORKERS

Years of Exposure	Time from onset of exposure (years) 0-4	5-9	10-14	15-19	20-24	25-29	30+	TOTAL
				EXPECTED DEATHS				
<5	1.447	1.257	1.251	1.056	.919	.720	.473	7.123
5-9		.508	.419	.401	.376	.370	.257	2.331
10-14			.655	.287	.275	.288	.261	1.766
15-19				.519	.292	.267	.252	1.329
20-24					.334	.251	.180	.765
25+						.177	.249	.426
TOTALS	1.447	1.765	2.325	2.263	2.196	2.073	1.672	13.780
				OBSERVED DEATHS				
<5	4	1			1			6
5-9			1	1		1	1	4
10-14			1	1				2
15-19				2				2
20-24					2	1	2	5
25+								0
TOTALS	4	1	2	4	3	2	3	19

Table 27a

EXPECTED AND OBSERVED DEATHS FOR CANCER OF THE LYMPHATIC SYSTEM AMONG FEMALE PCB WORKERS

Years of Exposure	Time from onset of exposure (years) 0-4	5-9	10-14	15-19	20-24	25-29	30+	TOTAL
				EXPECTED DEATHS				
<5	.405	.368	.389	.353	.326	.271	.187	2.299
5-9		.135	.101	.095	.099	.107	.081	.618
10-14			.148	.066	.075	.081	.094	.463
15-19				.112	.073	.071	.081	.338
20-24					.083	.057	.047	.187
25+						.049	.080	.130
TOTAL	.405	.503	.638	.626	.656	.636	.570	4.036
				OBSERVED DEATHS				
<5	3	1			1			5
5-9						1	1	2
10-14				1				1
15-19								0
20-24					1			1
25+								0
TOTAL	3	1	0	1	2	1	1	9

Table 27b

EXPECTED AND OBSERVED DEATHS FOR CANCER OF THE LYMPHATIC SYSTEM AMONG MALE PCB WORKERS

Year of Exposure	Time from onset of exposure (years) 0-4	5-9	10-14	15-19	20-24	25-29	30+	TOTAL
				EXPECTED DEATHS				
<5	.369	.359	.338	.275	.231	.161	.096	1.831
5-9		.152	.142	.143	.125	.112	.069	.744
10-14			.236	.104	.091	.091	.059	.582
15-19				.200	.099	.088	.065	.441
20-24					.121	.096	.062	.276
25+						.057	.079	.136
TOTAL	.369	.511	.716	.722	.667	.605	.430	4.010
				OBSERVED DEATHS				
<5								0
5-9			1	1				2
10-14								0
15-19								0
20-24						1	1	2
25+								0
TOTAL	0	0	1	1	0	1	1	4

TABLE 28

DEVELOPMENT OF ESTIMATED RELATIVE RISK CATEGORIES FOR CANCERS OF THE LYMPHATIC AND HEMATOPOIETIC SYSTEM

Hypothetical relative risk	Number of deaths in cell		Number of deaths in relative risk category	
	Expected	Observed	Expected	Observed
100	1.447	4 (1)		
103	.473			
104	.720		2.640	4 (1)
106	.919	1		
108	1.056			
110	.257	1	2.232	2
111	1.257, 1.251	1		
114	.370	1		
116	.508		3.386	2
120	.261, .376			
129	.288, .401	1		
135	.252			
136	.419	1		
141	.275			
145	.655	1 (1)	2.927	3 (1)
150	.267			
154	.287	1		
156	.180	2 (1)		
158	.519	2 (2)		
167	.292			
170	.334	2 (1)		
176	.251	1		
179	.177			
182	.249		2.556	8 (4)

( ) indicates number of cases in cell or category that are leukemias

Table 28a

DEVELOPMENT OF ESTIMATED RELATIVE RISK CATEGORIES FOR CANCERS OF THE LYMPHATIC SYSTEM AMONG FEMALE PCB WORKERS

Hypothetical relative risk	Number of deaths in cell		Number of deaths in relative risk category	
	Expected	Observed	Expected	Observed
100	.405	3		
103	.187			
104	.271		.863	3
106	.326	1		
108	.353			
110	.081	1	.760	2
111	.368,.389	1		
114	.107	1	.864	2
116	.508			
120	.099 .094			
129	.095 .081			
135	.081			
136	.101			
141	.075		.761	0
145	.148			
150	.071			
154	.066	1		
156	.047			
158	.112			
167	.073			
170	.083	1		
176	.057			
179	.049			
182	.080		.786	2

Table 28b

DEVELOPMENT OF ESTIMATED RELATIVE RISK CATEGORIES
FOR CANCERS OF THE LYMPHATIC SYSTEM AMONG MALE PCB WORKERS

Hypothetical relative risk	Number of deaths in cell Expected	Observed	Number of deaths in relative risk category Expected	Observed
100	.369			
103	.096			
104	.161			
106	.231		.857	0
108	.275			
110	.069			
111	.359		.703	0
111	.338			
114	.112			
116	.152			
120	.125,.059		.786	0
129	.143,.091	1		
135	.065			
136	.142	1		
141	.091			
145	.236			
150	.088		.856	2
154	.104			
156	.062	1		
158	.200			
167	.099			
170	.121			
176	.096	1		
179	.057			
182	.079		.816	2

TABLE 29

OBSERVED AND EXPECTED COHORT DEATHS AMONG FIVE COHORTS OF PCB EXPOSED CAPACITOR MANUFACTURING WORKERS ACCORDING TO TIME FROM ONSET OF EXPOSURE AND AGE AT FIRST EXPOSURE

ALL CANCER

	Time from onset of exposure					
	0-9	10-19	20-29	30+	Total 20+ years	Total All years
Age at first exposure: <25 years						
Observed	6	6	9	5	14	26
Expected	4.84	8.73	10.79	5.50	16.29	29.86
SMR	**124**	**69**	**83**	**91**	**86**	**87**
Age at first exposure: 25-34 years						
Observed	4	7	13	4	17	28
Expected	2.74	8.53	14.86	7.20	22.06	33.32
SMR	**146**	**82**	**87**	**56**	**77**	**84**
Age at first exposure: 35+ years						
Observed	16	31	26	2	28	75
Expected	14.55	26.64	26.67	8.39	35.06	76.21
SMR	**110**	**116**	**98**	**24**	**80**	**98**
Age at first exposure: all ages						
Observed	26	44	48	11	59	129
Expected	22.13	43.90	52.32	21.09	73.37	139.40
SMR	**117**	**100**	**92**	**52**	**80**	**93**

TABLE 30

OBSERVED AND EXPECTED COHORT DEATHS AMONG FIVE COHORTS OF PCB EXPOSED CAPACITOR MANUFACTURING WORKERS ACCORDING TO TIME FROM ONSET OF EXPOSURE AND AGE AT FIRST EXPOSURE

COLON AND RECTAL CANCER

	Time from onset of exposure					
	0-9	10-19	20-29	30+	Total 20+years	Total All years
Age at first exposure: <25 years						
Observed	0	0	0	1	1	1
Expected	0.45	0.88	1.13	0.65	1.77	3.11
SMR	**00**	**00**	**00**	**155**	**56**	**32**
Age at first exposure: 25-34 years						
Observed	1	1	3	1	4	6
Expected	0.25	0.52	1.67	0.93	2.60	3.66
SMR	**405**	**193**	**180**	**107**	**154**	**164**
Age at first exposure: 35+ years						
Observed	2	5	3	0	3	10
Expected	1.61	3.44	3.99	1.41	5.40	10.45
SMR	**124**	**145**	**75**	**00**	**56**	**96**
Age at first exposure: all ages						
Observed	3	6	6	2	8	17
Expected	1.31	4.84	6.79	2.99	9.77	17.22
SMR	**229**	**124**	**88**	**67**	**82**	**99**

TABLE 31

OBSERVED AND EXPECTED COHORT DEATHS AMONG FIVE COHORTS OF PCB EXPOSED CAPACITOR MANUFACTURING WORKERS ACCORDING TO TIME FROM ONSET OF EXPOSURE AND AGE AT FIRST EXPOSURE

LUNG CANCER

	Time from onset of exposure					
	0-9	10-19	20-29	30+	Total 20+ years	Total All years
Age at first exposure: <25 years						
Observed	0	0	1	1	2	2
Expected	0.22	0.85	2.01	1.15	3.16	4.24
SMR	00	00	50	87	63	47
Age at first exposure: 25-34 years						
Observed	1	1	2	1	3	5
Expected	0.26	1.58	3.90	1.94	5.84	7.69
SMR	385	63	51	52	51	65
Age at first exposure: 35+ years						
Observed	2	6	9	1	10	16
Expected	2.95	6.07	6.48	1.94	8.42	17.45
SMR	68	99	139	52	119	92
Age at first exposure: all ages						
Observed	3	7	12	3	15	25
Expected	3.43	8.51	12.40	5.03	17.43	29.38
SMR	87	82	97	60	86	85

TABLE 32

OBSERVED AND EXPECTED COHORT DEATHS AMONG FIVE COHORTS OF PCB EXPOSED CAPACITOR MANUFACTURING WORKERS ACCORDING TO TIME FROM ONSET OF EXPOSURE AND AGE AT FIRST EXPOSURE

FEMALE BREAST CANCER

	Time from onset of exposure					
	0-9	10-19	20-29	30+	Total 20+ years	Total All years
Age at first exposure: <25 years						
Observed	1	1	3	0	3	5
Expected	0.34	1.34	1.95	1.04	2.99	4.66
SMR	**294**	**75**	**153**	**00**	**100**	**107**
Age at first exposure: 25-34 years						
Observed	0	2	2	1	3	5
Expected	0.42	1.53	2.16	0.86	3.02	4.96
SMR	**00**	**131**	**93**	**116**	**99**	**101**
Age at first exposure: 35+ years						
Observed	1	4	1	0	1	6
Expected	1.94	2.74	2.40	0.61	3.01	7.70
SMR	**52**	**146**	**42**	**00**	**33**	**78**
Age at first exposure: all ages						
Observed	2	7	6	1	7	16
Expected	2.70	5.61	6.51	2.51	9.02	17.32
SMR	**74**	**125**	**92**	**40**	**78**	**92**

TABLE 33

OBSERVED AND EXPECTED COHORT DEATHS AMONG FIVE COHORTS OF PCB EXPOSED CAPACITOR MANUFACTURING WORKERS ACCORDING TO TIME FROM ONSET OF EXPOSURE AND AGE AT FIRST EXPOSURE

LEUKEMIA AND LYMPHATIC CANCER

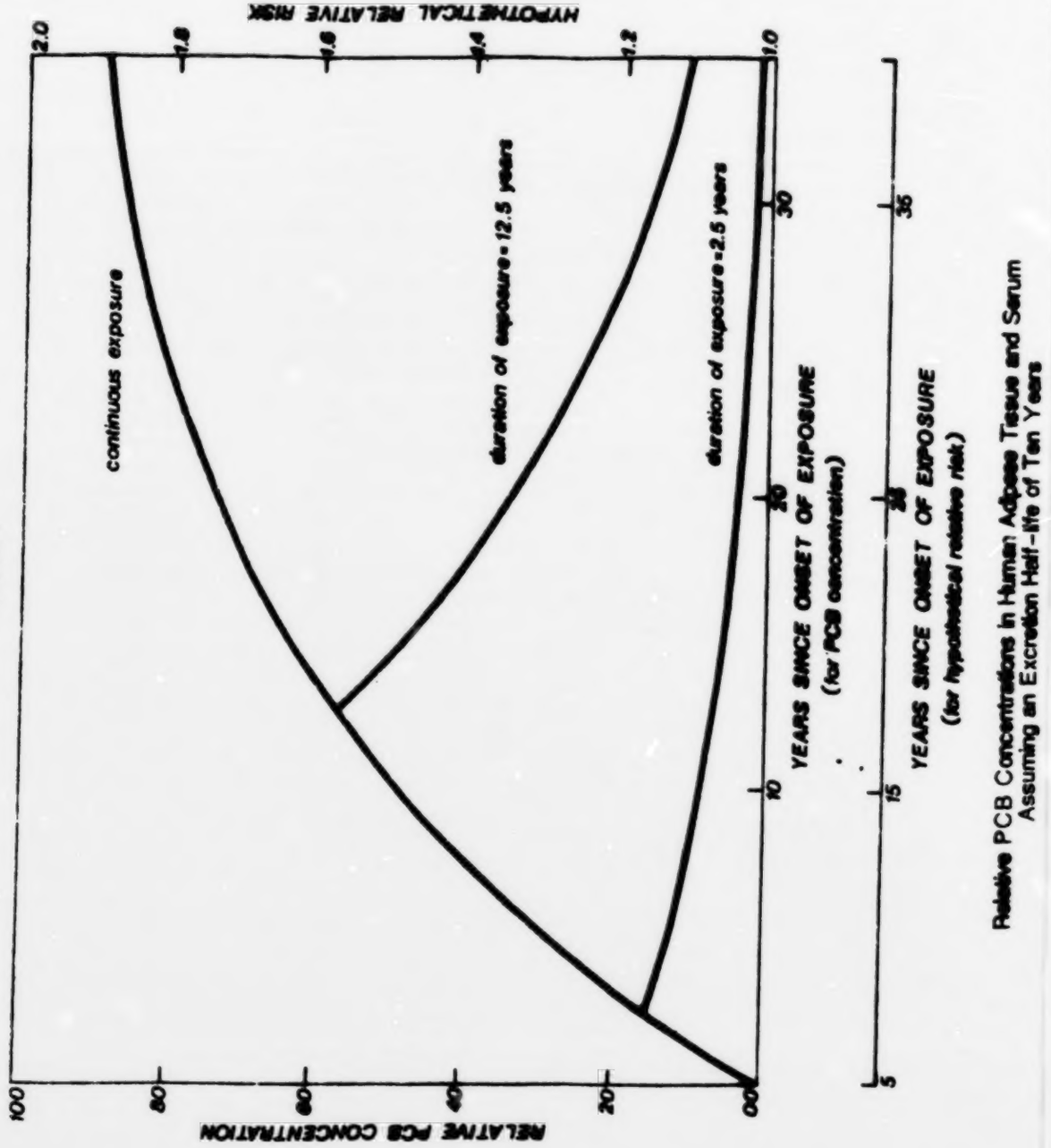
	Time from onset of exposure					
	0-9	10-19	20-29	30+	Total 20+ years	Total All years
Age at first exposure: <25 years						
Observed	2	2	2	1	3	6
Expected	1.50	1.60	1.03	0.42	1.45	4.55
SMR	**133**	**125**	**194**	**238**	**207**	**132**
Age at first exposure: 25-34 years						
Observed	1	1	1	1	2	4
Expected	0.50	0.82	1.09	0.51	1.60	2.93
SMR	**200**	**122**	**92**	**196**	**125**	**137**
Age at first exposure: 35+ years						
Observed	2	3	3	1	4	9
Expected	1.22	2.15	2.16	0.74	2.90	6.27
SMR	**164**	**140**	**139**	**135**	**138**	**144**
Age at first exposure: all ages						
Observed	5	6	5	3	8	19
Expected	3.22	4.57	4.28	1.67	5.95	13.74
SMR	**155**	**131**	**117**	**180**	**134**	**138**

FIGURE CAPTIONS

1. Relative PCB concentrations in human adipose tissue and serum assuming an excretion half-life of 10 years. Three different durations of exposure are shown. The model for cancer risk used in this review assumes any risk from I B cancer promotion activity will be proportional to the PCB body burden five years previously. A hypothetical relative risk of 2.0 was assumed as in Table 21.

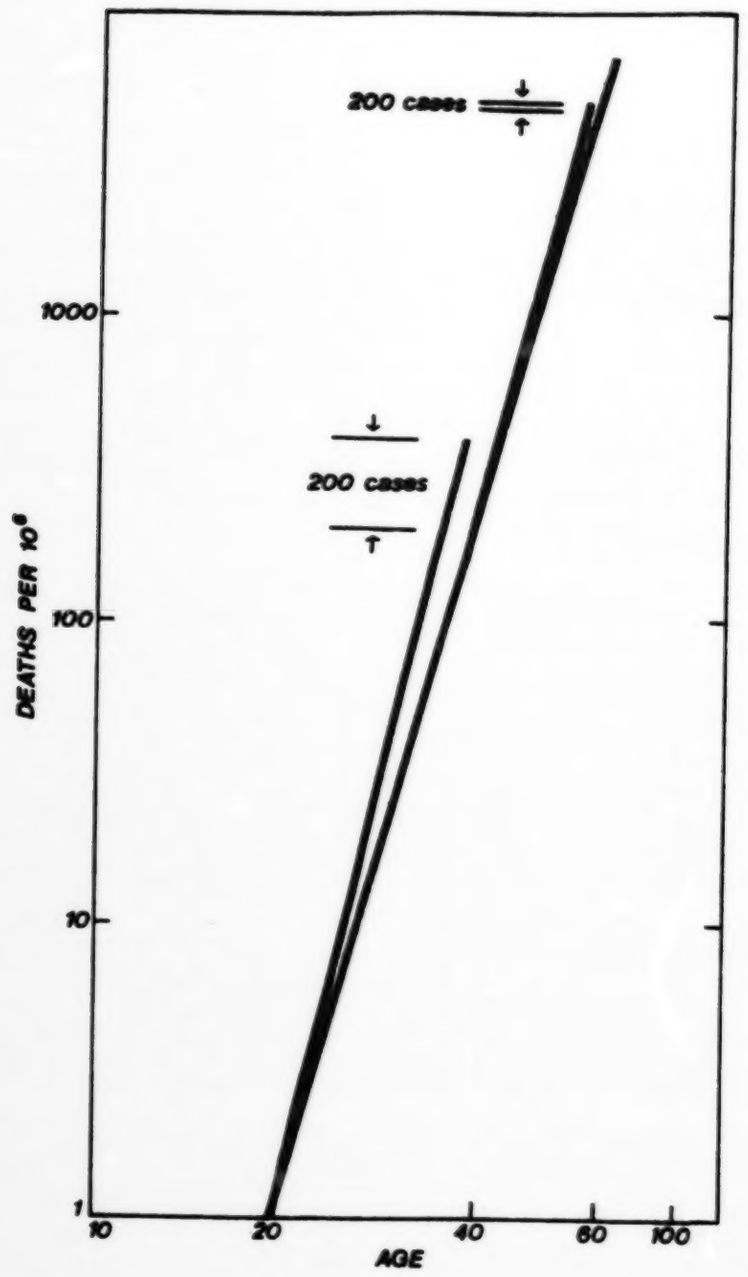
2. The hypothetical effect of PCBs on cancer initiation (through the stimulation of liver enzymes). The main line, extending from 20 to 60 years, is the hypothetical risk of cancer at a site of interest in the general population. The two shorter lines, beginning at 20 and 40 years of age, depict a PCB-related increase of 200 additional deaths per million population after 20 years exposure. The difference in effect among people first exposed at age 20 and those first exposed at age 40 is in the ratio of observed deaths to those expected in the general population, the two SMRs. In this example, the SMR for those exposed at age 20 is 200 (400/200) and for those exposed at age 40 is 104 (5200/5000).

FIGURE 1



Relative PCB Concentrations in Human Adipose Tissue and Serum
Assuming an Excretion Half-life of Ten Years

FIGURE 2



The Hypothetical Effect of PCBs on Cancer Initiation

APPENDIX B

EVIDENTIARY SOURCE INFORMATION

ON

OCCUPATIONAL EXPOSURE TO PCBs

APPENDIX B

Evidentiary Source Information on Occupational Exposure to PCBs

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APPENDIX C

CONCERNING PCB USAGE IN ONTARIO

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1.0 INTRODUCTION

1.1 Polychlorinated biphenyls (PCBs) are members of a broad family of organic chemicals known as chlorinated hydrocarbons. Produced synthetically, PCBs are the result of one or more chlorine atoms attaching themselves to a biphenyl molecule. The product is a liquid which is highly stable, non-corroding, relatively nonflammable, and which has good thermal properties.

1.2 Initially synthesized in 1881, PCBs were not produced on a commercial scale in the United States until 1929 (in 1954 in Japan). There were a variety of companies producing PCBs under various brand names. In North America most were marketed under the name Aroclor which contained varying amounts of chlorine content from 21 to 68 per cent as indicated by the last two digits in the trade name (e.g. Aroclor 1254 contained 54 percent chlorine (OME84: p.14)). Production was curtailed in the late seventies.

2.0 EXISTING MATERIAL DISTRIBUTION

2.1 According to a 1984 national inventory of PCBs compiled by Environment Canada, there are 9359 tonnes of PCBs extant in Ontario which comprises 46.7 per cent of the Canadian total (EC85: p.10).

2.2 Given its excellent thermal properties, the majority of PCB use in Ontario is for electrical applications, particularly dielectric fluids-- transformers (85%), capacitors (6.9%), and other (0.7%). Hydraulic fluid accounts for 0.08% of the use. Storage accounts for 7.1 per cent (EC85: p.10).

2.3 After July 1,1980, PCBs were prohibited for new applications in electrical transformers, capacitors, and associated electrical equipment. However, since transformers have a service life of 30 to 40 years, and capacitors have a life of 10 to 20 years, the vast majority of PCBs that were in use in Ontario before the 1980 prohibition are still in use today.

2.4 Askarel is the generic name given to the dielectric fluid containing PCBs, regardless of trade name. PCBs make up between 40 to 70 per cent of the content of Askarels together with a solvent (often trichlorobenzene). This is by far the major source of possible contamination.

2.5 A Ministry of Environment report (OME84: p.3) states that the second largest source of PCBs is low level concentrations which have contaminated the mineral oil of many non-Askarel transformers. A statistical sampling by Ontario Hydro indicates that 95 per cent of their mineral oil contains less than 50 ppm PCBs. Given this fact and some available U.S. data, the breakdown on PCB material has been derived as follows:

	Total liquid volume in tonnes	PCB content in tonnes
Askarel units	9,500	6,700
Mineral oil units	528,200(est)	8

2.6 Aside from Askarel in liquid storage, remaining PCBs consist of contaminated solids in storage -- clothing, tools, and soil contaminated from spills. This tonnage is comparatively small.

3.0 WORKER EXPOSURE TO PCBs

3.1 TRANSFORMER PRODUCTION

3.1.1 Through discussions with workers involved in building transformers in Ontario and through field visit reports of the Ministry of Labour, the following picture emerges of the general work processes involved in making transformers. Actual processes varied somewhat depending upon the workplace and the type of transformer being built. The processes were as follows:

1. Two types of transformer cores were commonly used: lock wound and stacked. Operations in the assembly area included stacking and coil winding, and high and low voltage tests. After testing, the cores were then heated and dried for a period of 1 to 5 days;

2. After drying, the core was lowered into its enclosure, mounted, and connected;

3. The transformer was then filled under vacuum with dielectric fluid, pressurized and tested;

4. Some dielectric fluid was drained, hookups were made and further testing was done. If required, the transformer was disassembled for repairs;

5. The transformer was topped up with dielectric fluid and sealed.

3.1.2 Given the absence of current hygiene practices when handling PCB-laden components during such production processes, it was quite likely that PCB exposures occurred through either the respiratory, dermal, or oral routes.

3.2 TRANSFORMER MAINTENANCE AND REPAIR

3.2.1 It is not correct to view transformers as sealed containers of PCBs from which worker exposure and environmental contamination are non-existent once produced. Transformers undergo frequent fluctuations in temperature which in turn creates stress on gaskets, welds, and bushings. As a result transformers often leak and/or breakdown.

3.2.2 Regarding transformer maintenance and repair, the major worker tasks leading to possible PCB exposures are as follows:

- fire/explosion/spill/leakage cleanup;
- draining and pumping transformer oil;
- replacing defective parts;
- topping off transformer oil;
- filtering transformer oil;
- retesting the transformer (Le87: p.259).

3.2.3 Worker exposure can fall into one of two categories. Primary exposure results from contact at the actual job site (i.e. with parts contaminated by PCBs); and secondary worker exposure results from contact with contaminated materials remote from a job site (i.e. the use of PCB-laden tools or clothes in a non-contaminated area) (Le87: p.260).

3.2.4 Some studies (Le87; NIOSH77; WHO76) have suggested that the dermal/oral route, rather than the respiratory, may be the principal pathway for exposures, leading to PCB body burdens among transformer maintenance and repair personnel. The possible sources of dermal exposure are as follows:

direct handling(without gloves) of contaminated transformer parts;

- direct handling of contaminated tools, pumps, hoses and test equipment;
- failure to wear protective clothing;
- failure to clean tools before returning them to tool boxes;
- failure to clean pumps, hoses, and test equipment after each use;
- improper storage of respirators in contaminated areas and with contaminated personal protective equipment;
- improper glove and coverall removal techniques;
- reuse of contaminated personal protective clothing upon leaving contaminated areas;
- failure to remove contaminated protective clothing upon leaving contaminated areas;
- failure to wash hands, forearms and face before smoking, eating or drinking outside of contaminated areas (dermal/oral component);
- cigarette smoking during work in contaminated areas (dermal/oral component);
- eating and drinking in contaminated areas (dermal/oral component);
- failure to use showers and clean/dirty locker rooms provided;
- wearing work clothes and shoes home;
- laundering work clothes at home (Le87: p.260).

3.3 CAPACITOR MANUFACTURING

3.3.1 Through a reading of the literature (Br81: p.121), and discussions with workers who produced capacitors in Ontario, the following picture of the general work processes involved in the construction of capacitors emerges. As was the case with transformers, processes varied slightly depending upon the type of capacitor being constructed, and the actual workplace under consideration.

1. Winding and Pre-Assembly

The inner components composed of paper, foil, and sometimes plastic film were wound together and loaded into metal casings. This was ordinarily done in a dust-free environment and, if physically separated from subsequent production processes, the chances of worker exposure to PCBs during this stage were minimal.

2. Impregnation

The preassembled capacitors were filled or impregnated with PCBs. This involved feeding the impregnator with PCBs, and

moving filled capacitors to the final stages of completion. The potential for PCB exposure during this process was very high.

3. **Final assembly**

The tops of the capacitors were closed by crimping, rubber stoppers, or soldering. The capacitors were then washed through a detergent or a degreaser such as trichloroethylene. They were then sent to dry, were painted and finally shipped. In the closing and washing of capacitors, there was possibility for exposure which was dependent upon the work processes used.

4. **Testing**

Before being shipped, capacitors were tested. There was possibility for explosions and/or leakage during this stage, and hence the potential for exposure.

3.4 CAPACITOR MAINTENANCE AND REPAIR

3.4.1 Askarel-filled capacitors are hermetically sealed units and ordinarily there is little provision for internal maintenance. Therefore defective capacitors are ordinarily not repaired. Most capacitors are equipped with fusing to "de-energize" themselves. However, in abnormal situations, capacitors have been known to open and sometimes spill their contents, and as a result, the possibility for exposure in the removal and storage of defective capacitors exists.

3.4.2 During the maintenance of capacitors, workers may be exposed while cleaning up leaking or weeping capacitors. Leakage, or weep, may occur from the tank, radiator fins, top cover (if gasketed), manhole covers, top or bottom drain spout, and high and low voltage bushings (EC82: p.17).

3.4.3 Many of the modes of dermal exposure which apply to transformer maintenance and repair workers also apply to capacitor maintenance staff.

4.0 EVALUATION CRITERIA

4.1 The following criteria may be used to evaluate the degree of worksite contamination to PCBs (MOL86: p.31-32):

1. Skin contact potential based on the nature of the site of the PCB contamination and its potential for, and frequency of, contact;

2. Duration of potential skin contact;

3. Air sampling in the vicinity of possible PCB contamination;

4. Although there are variances in the accuracy of various methods (Na85: p.132-140), swipe samples of the site can be used to determine the degree and extent of surface contamination;

5. Follow-up swipe samples to evaluate the effectiveness of the decontamination of the site.

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